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(54) **Title:** MUSCARINIC RECEPTOR ANTAGONISTS

(57) **Abstract:** This present invention generally relates to muscarinic receptor antagonists, which are useful, among other uses, for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems mediated through muscarinic receptors. The invention also relates to the process for the preparation of disclosed compounds, pharmaceutical compositions containing the disclosed compounds, and the methods for treating diseases mediated through muscarinic receptors.

MUSCARINIC RECEPTOR ANTAGONISTS

Field of the Invention

This present invention generally relates to muscarinic receptor antagonists, which are useful, among other uses, for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems mediated through muscarinic receptors. The invention also relates to the process for the preparation of disclosed compounds, pharmaceutical compositions containing the disclosed compounds, and the methods for treating diseases mediated through muscarinic receptors.

Background of the Invention

Muscarinic receptors as members of the G Protein Coupled Receptors (GPCRs) are composed of a family of 5 receptor sub-types (M_1, M_2, M_3, M_4 and M_5) and are activated by the neurotransmitter acetylcholine. These receptors are widely distributed on multiple organs and tissues and are critical to the maintenance of central and peripheral cholinergic neurotransmission. The regional distribution of these receptor sub-types in the brain and other organs has been documented. (for example,, the M_1 subtype is located primarily in neuronal tissues such as cereberal cortex and autonomic ganglia, the M_2 subtype is present mainly in the heart where it mediates cholinergically induced bradycardia, and the M_3 subtype is located predominantly on smooth muscle and salivary glands (*Nature*, 323, p.411 (1986); *Science*, 237, p.527 (1987)).

A review in *Current Opinions in Chemical Biology*, 3, p. 426 (1999), as well as in *Trends in Pharmacological Sciences*, 22, p. 409 (2001) by Eglen et. al., describes the biological potentials of modulating muscarinic receptor subtypes by ligands in different disease conditions, such as Alzheimer's Disease, pain, urinary disease condition, chronic obstructive pulmonary disease, and the like.

A review in *J. Med. Chem.*, 43, p. 4333 (2000), by Felder et. al. describes therapeutic opportunities for muscarinic receptors in the central nervous system and elaborates on muscarinic receptor structure and function, pharmacology and their therapeutic uses.

The pharmacological and medical aspects of the muscarinic class of acetylcholine agonists and antagonists are presented in a review in *Molecules*, 6, p. 142 (2001).

Birdsall et. al. in *Trends in Pharmacological Sciences*, 22, p. 215 (2001) have also summarized the recent developments on the role of different muscarinic receptor subtypes using different muscarinic receptor of knock out mice.

Muscarinic agonists such as muscarine and pilocarpine and antagonists such as atropine have been known for over a century, but little progress has been made in the discovery of receptor subtype-selective compounds, making it difficult to assign specific functions to the individual receptors. Although classical muscarinic antagonists such as atropine are potent bronchodilators, their clinical utility is limited due to high incidence of both peripheral and central adverse effects such as tachycardia, blurred vision, dryness of mouth, constipation, dementia, etc. Subsequent development of the quarterly derivatives of atropine such as ipratropium bromide are better tolerated than parenterally administered options, but most of these are not ideal anti-cholinergic bronchodilators, due to lack of selectivity for muscarinic receptor sub-types, resulting in dose-limiting side-effects such as thirst, nausea, mydriasis and those associated with the heart such as tachycardia mediated by the M_2 receptor.

Annual Review of Pharmacological Toxicol., 41, p. 691 (2001), describes the pharmacology of the lower urinary tract infections. Although anti-muscarinic agents such as oxybutynin and tolterodine that act non-selectively on muscarinic receptors have been used for many years to treat bladder hyperactivity, the clinical effectiveness of these agents has been limited due to the side effects such as dry mouth, blurred vision and constipation. Tolterodine is considered to be generally better tolerated than oxybutynin. (Steers et. al., in *Curr. Opin. Invest. Drugs*, 2, 268; Chapple et. al., in *Urology*, 55, 33; Steers et al., Adult and Pediatric Urology, ed. Gillenwatteret al., pp 1220-1325, St. Louis, MO; Mosby. 3rd edition (1996)).

There remains a need for development of new highly selective muscarinic antagonists which can interact with distinct subtypes, thus avoiding the occurrence of adverse effects.

Compounds having antagonistic activity against muscarinic receptors have been described in Japanese patent application Laid Open Number 92921/1994 and 135958/1994; WO 93/16048; U.S. Patent No. 3,176,019; GB 940,540; EP 0325 571; WO 98/29402; EP 0801067; EP 0388054; WO 9109013; U.S. Patent No. 5,281,601. Also, U.S. Patent Nos. 6,174,900, 6,130,232 and 5,948,792; WO 93/16018 and WO96/33973 are other references of interest; WO 97/45414 are related to 1,4-disubstituted piperidine derivatives; WO 98/05641 describes fluorinated, 1,4-disubstitued piperidine derivatives; U. S. Patent No. 5,397,800 discloses 1-azabicyclo[2.2.1]heptanes. U.S. Patent No.5, 001,160 describes 1-aryl-1-hydroxy-1-substituted-3-(4-substituted-1-piperazinyl)-2-propanones. WO 99/43657 describes 2-arylethyl-(piperidin-4-ylmethyl)amine derivatives as muscarinic receptors antagonists. WO 01/090082 describes substituted 1-amino-alkyl lactams and their use as muscarinic receptor antagonists. WO 01/47893 describes azabicycloctane derivatives useful in the treatment of cardiac arrhythmias. WO 01/42213 describes 2-biphenyl-4-piperidinyl ureas. WO 01/42212 describes carbamate derivatives. WO 01/90081 describes amino alkyl lactam. WO 02/53564 describes novel quinuclidine derivatives. WO 02/00652 describes carbamates derived from arylalkyl amines. WO 02/06241 describes 1,2,3,5-tetrahydrobenzo(c)azepin-4-one derivatives. U.S. application No. 20030105071 describes thiazole and other heterocyclic ligands for mammalian dopamine, muscarinic and serotonic receptors and transporters, and method of use thereof. WO 03/033495 describes quinuclidine derivatives and their use as M_2 and/or M_3 muscarinic receptor antagonists. US2003/0171362 describes amino-tetralin derivatives as muscarinic receptor antagonists. US2003/0162780 describes 4-piperidinyl alkyl amine derivatives as muscarinic receptor antagonists. U.S. 5,179,108 disclose derivatives of 4-(aminomethyl) piperidine and their therapeutic applications. WO 03/048125 discloses aminotetralin derivatives as muscarinic receptor antagonists. WO 03/048124 discloses 4-piperidinyl alkylamine derivatives as muscarinic receptor antagonists. WO 2004/052857 and WO 04/004629 disclose 3,6-disubstituted azabicyclo [3.1.0] hexane derivatives useful as muscarinic receptor antagonists. WO 04/005252 discloses azabicyclo derivatives as musacrinic receptor antagonists. discloses WO 04/014853, WO 04/067510 and WO 04/014363 disclose derivatives of 3,6-disubstituted azabicyclohexane useful as muscarinic receptor antagonists. WO 2004/056810 discloses xanthine derivatives as muscarinic receptor antagonists. WO 2004/056811 discloses flaxavate derivatives as muscarinic

receptor antagonists. WO 2004/056767 discloses 1-substituted-3-pyrrolidine derivatives as muscarinic receptor antagonists. WO 2004/018422 disclose fluoro and sulphonylamino containing 3,6-disubstituted azabicyclo[3.1.0] hexane derivatives as muscarinic receptor antagonists.

J.Med.Chem., 44, p. 984 (2002), describes cyclohexylmethylpiperidinyl-triphenylpropioamide derivatives as selective M_3 antagonist discriminating against the other receptor subtypes. *J.Med.Chem.*, 36, p. 610 (1993), describes the synthesis and antimuscarinic activity of some 1-cycloalkyl-1-hydroxy-1-phenyl-3-(4-substituted piperazinyl)-2-propanones and related compounds. *J.Med.Chem.*, 34, p.3065 (1991), describes analogues of oxybutynin, synthesis and antimuscarinic activity of some substituted 7-amino-1-hydroxy-5-heptyn-2-ones and related compounds.

Summary of the Invention

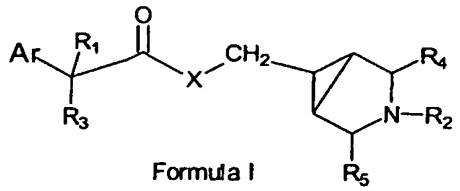
In one aspect, there are provided muscarinic receptor antagonists, which can be useful as safe and effective therapeutic or prophylactic agents for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems. Also provided are processes for synthesizing such compounds.

In another aspect, pharmaceutical compositions containing such compounds are provided together with acceptable carriers, excipients or diluents which can be useful for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems.

The enantiomers, diastereomers, N-oxides, polymorphs, pharmaceutically acceptable salts and pharmaceutically acceptable solvates of these compounds as well as metabolites having the same type of activity are also provided, as well as pharmaceutical compositions comprising the compounds, their metabolites, enantiomers, diastereomers, N-oxides, polymorphs, solvates or pharmaceutically acceptable salts thereof, in combination with a pharmaceutically acceptable carrier and optionally included excipients.

Other aspects will be set forth in the description which follows, and in part will be apparent from the description or may be learnt by the practice of the invention.

In accordance with one aspect, there are provided compounds having the structure of Formula I



Formula I

and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, metabolites, wherein

R_1 can be hydrogen, lower (C_1-C_6) alkyl, lower (C_2-C_7) alkenyl, lower (C_2-C_7) alkynyl, cycloalkyl, amino, substituted amino, -OR_z {wherein R_z is selected from, for example, hydrogen, -$Si(CH_3)_3$, lower (C_1-C_6) alkyl, lower (C_2-C_6) alkenyl, lower (C_2-C_6) alkynyl, cycloalkyl, aryl, and -$C(=O)NHR_r$ (wherein R_r is selected from, for example, hydrogen, lower (C_1-C_6) alkyl, lower (C_2-C_6) alkenyl, lower (C_2-C_6) alkynyl, aryl, and cycloalkyl)}.

R_2 can be carboxy, -SO_2R_6 {wherein R_6 is selected from, for example, alkyl, alkenyl, alkynyl, cycloalkyl, -NR_pR_q (wherein R_p and R_q are selected from, for example, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, and heteroarylalkyl), aryl, aralkyl, heteroaryl, heterocyclyl, heterocyclylalkyl, and heteroarylalkyl, or R_p and R_q may also together join to form a heterocyclyl ring}, -$C(=O)OR_7$ (wherein R_7 is selected from, for example, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and aralkyl), -$C(=O)NR_xR_y$ {wherein R_x and R_y are each independently selected from, for example, hydrogen, hydroxy (as restricted by the definition that both R_x and R_y cannot be hydroxy at the same time), alkyl, alkenyl, alkynyl, aryl, aralkyl, $S(O)_2R_6$ wherein R_6 is the same as defined above, heteroaryl, heterocyclyl, heteroarylalkyl, and heterocyclylalkyl, or R_x and R_y may also together join to form a heterocyclyl ring}, acyl, halogen (F, Cl, Br, I), cyano, -NR_xR_y, wherein R_x and R_y are the same as defined above), or -$C(=O)CH_2OR_x$ (wherein R_x is the same as defined above).

R_3 can be alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, and heteroarylalkyl.

R_4 and R_5 can be independently selected from, for example, hydrogen, lower (C_1-C_6) alkyl, lower (C_2-C_7) alkenyl, and lower (C_2-C_7) alkynyl.

X can be oxygen, -NR_7 (wherein R_7 is selected from, for example, hydrogen, lower (C_1-C_6) alkyl, lower (C_2-C_7) alkenyl, lower (C_2-C_7) alkynyl, aralkyl, and aryl.

Ar can be aryl, heteroaryl, and heterocyclyl.

In accordance with a further aspect, there is provided a method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory, urinary and gastrointestinal systems, wherein the disease or disorder is mediated through muscarinic receptors. The method includes administration of at least one compound having the structure of Formula I.

In accordance with another aspect, there is provided a method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder associated with muscarinic receptors, comprising administering to a patient in need thereof, an effective amount of a muscarinic receptor antagonist compound as described above.

In accordance with yet a further aspect, there is provided a method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory system such as bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, and the like; urinary system which induce such urinary disorders as urinary incontinence, lower urinary tract symptoms (LUTS), etc.; and gastrointestinal system such as irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesis with compounds as described above, wherein the disease or disorder is associated with muscarinic receptors.

In accordance with yet another aspect, there are provided processes for preparing the compounds as described above.

The compounds described herein exhibit significant potency in terms of their activity, as determined by *in vitro* receptor binding and functional assays and *in vivo* experiments using anaesthetized rabbits. The compounds that were found active *in vitro* were tested *in vivo*. Some of the compounds are potent muscarinic receptor antagonists with high affinity towards M_3 receptors. Therefore, pharmaceutical compositions for the possible treatment for the disease or disorders associated with muscarinic receptors are provided. In addition, the compounds can be administered orally or parenterally.

The following definitions apply to terms as used herein

The term "alkyl," unless otherwise specified, refers to a monoradical branched or unbranched saturated hydrocarbon chain having from 1 to 20 carbon atoms. This term can be exemplified by groups such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, n-decyl, tetradecyl, and the like. Alkyl groups may be substituted further with one or more substituents selected from alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, carboxyalkyl, aryl, heterocyclyl, heteroaryl, arylthio, thiol, alkylthio, aryloxy, nitro, aminosulfonyl, aminocarbonylamino, -NHC(=O)R_f, -NR_fR_q, -C(=O)NR_fR_q, -NHC(=O)NR_fR_q,, -C(=O)heteroaryl, C(=O)heterocyclyl, -O-C(=O)NR_fR_q {wherein R_f and R_q are independently selected from alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl}, nitro, or -SO_2R_6 (wherein R_6 is alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl). Unless otherwise constrained by the definition, alkyl substituents may be further substituted by 1-3 substituents selected from alkyl, carboxy, -NR_fR_q, -C(=O)NR_fR_q, -OC(=O) NR_fR_q, -NHC(=O)NR_fR_q (wherein R_f and R_q are the same as defined earlier), hydroxy, alkoxy, halogen, CF_3, cyano, and $-SO_2R_6$, (wherein R_6 are the same as defined earlier); or an alkyl group also may be interrupted by 1-5 atoms of groups independently selected from oxygen, sulfur or -NR_a- {wherein R_a is selected from hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, acyl, aralkyl,-C(=O)OR_f (wherein R_f is the same as defined earlier), SO_2R_6 (where R_6 is as defined earlier), or -C(=O)NR_fR_q (wherein R_f and R_q are as defined earlier)}. Unless otherwise constrained by the definition, all substituents may be substituted further by 1-3 substituents selected from alkyl, carboxy, -NR_fR_q, -C (=O)NR_fR_q, -O-C(=O)NR_fR_q (wherein R_f and R_q are the same as defined earlier) hydroxy, alkoxy, halogen, CF_3, cyano, and $-SO_2R_6$ (where R_6 is same as defined earlier); or an alkyl group as defined above that has both substituents as defined above and is also interrupted by 1-5 atoms or groups as defined above.

The term "alkylene," as used herein, refers to a diradical branched or unbranched saturated hydrocarbon chain having from 1 to 6 carbon atoms and one or more hydrogen

can optionally be substituted with alkyl, hydroxy, halogen or oximes. This term can be exemplified by groups such as methylene, ethylene, propylene isomers (e.g., $-CH_2CH_2CH_2$ and $-CH(CH_3)CH_2$) and the like. Alkylene may further be substituted with one or more substituents such as alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, arylthio, thiol, alkylthio, aryloxy, heteroaryloxy, aminosulfonyl, $-COOR_2$ (wherein R_2 is the same as defined earlier), $-NHC(=O)R_x$, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-NHC(=O)NR_xR_y$, $-C(=O)$heteroaryl, $C(=O)$heterocyclyl, $-O-C(=O)NR_xR_y$ (wherein R_x and R_y are the same as defined earlier), nitro, $-S(O)_nR_3$ (wherein n and R_3 are the same as defined earlier). Unless otherwise constrained by the definition, all substituents may be further substituted by 1-3 substituents chosen from alkyl, carboxy, $-COOR_2$ (wherein R_2 is the same as defined earlier), $-NR_xR_y$, $-C(=O)NR_xR_y$, $-OC(=O)NR_xR_y$, $-NHC(=O)NR_xR_y$ (wherein R_x and R_y are the same as defined earlier), hydroxy, alkoxy, halogen, CF_3, cyano, and $-S(O)_nR_3$ (where R_3 and n are the same as defined earlier). Alkylene can also be optionally interrupted by 1-5 atoms of groups independently chosen from oxygen, sulfur and $-NR_a$, where R_a is chosen from hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, acyl, aralkyl, $-C(=O)OR_2$ (wherein R_2 is the same as defined earlier), $-S(O)_nR_3$ (where n and R_3 are the same as defined earlier), $-C(=O)NR_xR_y$ (wherein R_x and R_y are as defined earlier) -CONH-, -C=O or -C=NOH.

The term "alkenyl," unless otherwise specified, refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group having from 2 to 20 carbon atoms with cis, trans, or geminal geometry. In the event that alkenyl is attached to a heteroatom, the double bond cannot be alpha to the heteroatom. Alkenyl groups may be substituted further with one or more substituents selected from alkyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, $-NHC(=O)R_f$, $-NR_fR_q$, $-C(=O)NR_fR_q$, $-NHC(=O)NR_fR_q$, $-O-C(=O)NR_fR_q$ (wherein R_f and R_q are the same as defined earlier), alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, heterocyclyl, heteroaryl, heterocyclyl alkyl, heteroaryl alkyl, aminosulfonyl, aminocarbonylamino, alkoxyamino, nitro, or SO_2R_6 (wherein R_6 are is same as defined earlier). Unless otherwise constrained by the definition, alkenyl substituents optionally may be substituted further by 1-3 substituents

selected from alkyl, carboxy, hydroxy, alkoxy, halogen, $-CF_3$, cyano, $-NR_fR_q$, $-C(=O)NR_fR_q$, $-O-C(=O)NR_fR_q$ (wherein R_f and R_q are the same as defined earlier) and $-SO_2R_6$(where R_6 is same as defined earlier).

The term "alkenylene" unless otherwise specified, refers to a diradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 6 carbon atoms with cis, trans or geminal geometry. In the event that alkenylene is attached to the heteroatom, the double bond cannot be alpha to the heteroatom. The alkenylene group can be connected by two bonds to the rest of the structure of compound of Formula I. Alkenylene may further be substituted with one or more substituents such as alkyl, alkynyl, alkoxy, cycloalkyl, acyl, acylamino, acyloxy, $-NHC(=O)R_x$, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-NHC(=O)NR_xR_y$, $-OC(=O)NR_xR_y$ (wherein R_x and R_y are the same as defined earlier), alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, $-COOR_2$ (wherein R_2 is the same as defined earlier), arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, heterocyclyl, heteroaryl, heterocyclyl alkyl, heteroaryl alkyl, aminosulfonyl, alkoxyamino, nitro, $-S(O)_nR_3$ (where R_3 and n are the same as defined earlier). Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, $-COOR_2$ (wherein R_2 is the same as defined earlier), hydroxy, alkoxy, halogen, $-CF_3$, cyano, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-OC(=O)NR_xR_y$ (wherein R_x and R_y are the same as defined earlier) and $-S(O)_nR_3$ (where R_3 and n are the same as defined earlier).

The term "alkynyl," unless otherwise specified, refers to a monoradical of an unsaturated hydrocarbon, having from 2 to 20 carbon atoms. In the event that alkynyl is attached to a heteroatom, the triple bond cannot be alpha to the heteroatom. Alkynyl groups may be substituted further with one or more substituents selected from alkyl, alkenyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, aminosulfonyl, aminocarbonylamino, nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, $-NHC(=O)R_f$, $-NR_fR_q$, $-NHC(=O)NR_fR_q$, $-C(=O)NR_fR_q$, $-O-C(=O)NR_fR_q$ (wherein R_f and R_q are the same as defined earlier), or $-SO_2R_6$ (wherein R_6 is as defined earlier). Unless otherwise constrained by the definition, alkynyl substituents optionally may be substituted further by 1-3 substituents selected

from alkyl, carboxy, carboxyalkyl, hydroxy, alkoxy, halogen, CF_3, $-NR_fR_q$, $-C(=O)NR_fR_q$, $-NHC(=O)NR_fR_q$, $-C(=O)NR_fR_q$ (wherein R_f and R_q are the same as defined earlier), cyano, or $-SO_2R_6$ (where R_6 is same as defined earlier).

The term "alkynylene" unless otherwise specified, refers to a diradical of a triply-unsaturated hydrocarbon, preferably having from 2 to 6 carbon atoms. In the event that alkynylene is attached to the heteroatom, the triple bond cannot be alpha to the heteroatom. The alkenylene group can be connected by two bonds to the rest of the structure of compound of Formula I. Alkynylene may further be substituted with one or more substituents such as alkyl, alkenyl, alkoxy, cycloalkyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, aminosulfonyl, nitro, heterocyclyl, heteroaryl, heterocyclyl alkyl, heteroarylalkyl, $-NHC(=O)R_x$ $-NR_xR_y$, $-NHC(=O)NR_xR_y$, $-C(=O)NR_xR_y$, $-OC(=O)NR_xR_y$ (wherein R_x and R_y are the same as defined earlier), $-S(O)_nR_3$ (where R_3 and n are the same as defined earlier). Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, $-COOR_2$ (wherein R_2 is the same as defined earlier), hydroxy, alkoxy, halogen, CF_3, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-NHC(=O)NR_xR_y$, $-C(=O)NR_xR_y$ (wherein R_x and R_y are the same as defined earlier), cyano, and $-S(O)_nR_3$ (where R_3 and n are the same as defined earlier).

The term "cycloalkyl," unless otherwise specified, refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings, which may optionally contain one or more olefinic bonds, unless otherwise constrained by the definition. Such cycloalkyl groups can include, for example, single ring structures, including cyclopropyl, cyclobutyl, cyclooctyl, cyclopentenyl, and the like, or multiple ring structures, including adamantanyl, and bicyclo [2.2.1] heptane, or cyclic alkyl groups to which is fused an aryl group, for example, indane, and the like. Spiro and fused ring structures can also be included. Cycloalkyl groups may be substituted further with one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, carboxyalkyl, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, aminosulfonyl, aminocarbonylamino, $-NR_fR_q$, -NHC (=O) NR_fR_q, -NHC (=O) R_f, -C (=O)

NR_fR_q, -O-C(=O)NR_fR_q (wherein R_f and R_q are the same as defined earlier), nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, or SO_2-R_6 (wherein R_6 is same as defined earlier). Unless otherwise constrained by the definition, cycloalkyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, carboxy, hydroxy, alkoxy, halogen, CF_3, -NR_fR_q, -C(=O)NR_fR_q, -NHC(=O)NR_fR_q, -OC(=O)NR_fR_q (wherein R_f and R_q are the same as defined earlier), cyano or $-SO_2R_6$ (where R_6 is same as defined earlier). "Cycloalkylalkyl" refers to alkyl-cycloalkyl group linked through alkyl portion, wherein the alkyl and cycloalkyl are the same as defined earlier.

The term "alkoxy" denotes the group O-alkyl, wherein alkyl is the same as defined above.

The term "aryl," unless otherwise specified, refers to carbocyclic aromatic groups, for example, phenyl, biphenyl or napthyl ring and the like, optionally substituted with 1 to 3 substituents selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, acyl, aryloxy, CF_3, cyano, nitro, $COOR_e$ (wherein R_e is hydrogen, alkyl, alkenyl, cycloalkyl, aralkyl, heterocyclylalkyl, heteroarylalkyl), $NHC(=O)R_f$, -NR_fR_q, -C(=O)NR_fR_q, -NHC(=O)NR_fR_q, -O-C(=O)NR_fR_q (wherein R_f and R_q are the same as defined earlier), -SO_2R_6 (wherein R_6 is same as defined earlier), carboxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or amino carbonyl amino. The aryl group optionally may be fused with a cycloalkyl group, wherein the cycloalkyl group may optionally contain heteroatoms selected from O, N or S.

The term "aralkyl," unless otherwise specified, refers to alkyl-aryl linked through an alkyl portion (wherein alkyl is as defined above) and the alkyl portion contains 1-6 carbon atoms and aryl is as defined below. Examples of aralkyl groups include benzyl, ethylphenyl and the like.

The term "aralkenyl," unless otherwise specified, refers to alkenyl-aryl linked through alkenyl (wherein alkenyl is as defined above) portion and the alkenyl portion contains 1 to 6 carbon atoms and aryl is as defined below.

The term "aryloxy" denotes the group O-aryl, wherein aryl is as defined above.

The term "carboxy," as defined herein, refers to –C(=O)OH.

The term "heteroaryl," unless otherwise specified, refers to an aromatic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having from 8 to 10 ring atoms, with one or more heteroatom(s) independently selected from N, O or S optionally substituted with 1 to 4 substituent(s) selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, carboxy, aryl, alkoxy, aralkyl, cyano, nitro, heterocyclyl, heteroaryl, $-NR_fR_q$, CH=NOH, $-(CH_2)_wC(=O)R_g$ {wherein w is an integer from 0-4 and R_g is hydrogen, hydroxy, OR_f, NR_fR_q, $-NHOR_z$ or –NHOH}, $-C(=O)NR_fR_q$ and $-NHC(=O)NR_fR_q$, $-SO_2R_6$, $-O-C(=O)NR_fR_q$, $-O-C(=O)R_f$, $-O-C(=O)OR_f$ (wherein R_6, R_f and R_q are as defined earlier, and R_z is alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl). Unless otherwise constrained by the definition, the substituents are attached to a ring atom, *i.e.*, carbon or heteroatom in the ring. Examples of heteroaryl groups include oxazolyl, imidazolyl, pyrrolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, thiazolyl, oxadiazolyl, benzoimidazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, thienyl, isoxazolyl, triazinyl, furanyl, benzofuranyl, indolyl, benzothiazolyl, or benzoxazolyl, and the like.

The term 'heterocyclyl," unless otherwise specified, refers to a non-aromatic monocyclic or bicyclic cycloalkyl group having 5 to 10 atoms wherein 1 to 4 carbon atoms in a ring are replaced by heteroatoms selected from O, S or N, and optionally are benzofused or fused heteroaryl having 5-6 ring members and/or optionally are substituted, wherein the substituents are selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, aryl, alkoxy, alkaryl, cyano, nitro, oxo, carboxy, heterocyclyl, heteroaryl, $-O-C(=O)R_f$, $-O-C(=O)OR_f$, $-C(=O)NR_fR_q$, SO_2R_6, $-O-C(=O)NR_fR_q$, $-NHC(=O)NR_fR_q$, $-NR_fR_q$ (wherein R_6, R_f and R_q are as defined earlier) or guanidine. Heterocyclyl can optionally include rings having one or more double bonds. Unless otherwise constrained by the definition, the substituents are attached to the ring atom, *i.e.*, carbon or heteroatom in the ring. Also, unless otherwise constrained by the definition, the heterocyclyl ring optionally may contain one or more olefinic bond(s). Examples of heterocyclyl groups include oxazolidinyl, tetrahydrofuranyl, dihydrofuranyl, dihydropyridinyl, dihydroisoxazolyl, dihydrobenzofuryl, azabicyclohexyl, dihydroindolyl, pyridinyl, isoindole 1,3-dione, piperidinyl or piperazinyl.

"Heteroarylalkyl" refers to alkyl-heteroaryl group linked through alkyl portion, wherein the alkyl and heteroaryl are as defined earlier.

"Heterocyclylalkyl" refers to alkyl-heterocyclyl group linked through alkyl portion, wherein the alkyl and heterocyclyl are as defined earlier.

"Acyl" refers to –C(=O)R'' wherein R'' is selected from hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl.

"Alkylcarbonyl" refers to –C(=O)R'', wherein R'' is selected from alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl.

"Alkylcarboxy" refers to –O–C(=O)R'', wherein R'' is selected from alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl.

"Amine," unless otherwise specified, refers to $-NH_2$. "Substituted amine," unless otherwise specified, refers to $-N(R_k)_2$, wherein each R_k independently is selected from hydrogen {provided that both R_k groups are not hydrogen (defined as "amino")}, alkyl, alkenyl, alkynyl, aralkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heterocyclylalkyl, heteroarylalkyl, acyl, SO_2R_6 (wherein R_6 is as defined above), $-C(=O)NR_fR_q$, $NHC(=O)NR_fR_q$, or $-NHC(=O)OR_f$ (wherein R_f and R_q are as defined earlier).

"Amine," unless otherwise specified, refers to $-NH_2$. "Substituted amino" unless otherwise specified, refers to a group $-N(R_k)_2$ wherein each R_k is independently selected from the group hydrogen provided that both R_k groups are not hydrogen (defined as "amino"), alkyl, alkenyl, alkynyl, aralkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heterocyclylalkyl, heteroarylalkyl, acyl, $S(O)_mR_6$ (wherein m and R_6 is the same as defined above), $-C(=R_v)NR_xR_y$ (wherein R_v is O or S & R_x and R_y are the same as defined earlier) or $NHC(=R_v)NR_yR_x$ (wherein R_v, R_y and R_x are the same as defined earlier). Unless otherwise constrained by the definition, all amino substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, aralkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, carboxy, $-COOR_7$ (wherein R_7 is the same as defined earlier), hydroxy, alkoxy, halogen, CF_3, cyano, $-C(=R_v)NR_xR_y$ (wherein R_v is the same as defined

earlier), -O(C=O)NR_xR_y, –OC(=R_v)NR_xR_y (wherein R_x, R_y and R_v are the same as defined earlier), -$S(O)_mR_6$ (where R_6 and m is the same as defined above).

The term "leaving group" generally refers to groups that exhibit the desirable properties of being labile under the defined synthetic conditions and also, of being easily separated from synthetic products under defined conditions. Examples of such leaving groups includes but not limited to halogen (F, Cl, Br, I), triflates, tosylate, mesylates, alkoxy, thioalkoxy, hydroxy radicals and the like.

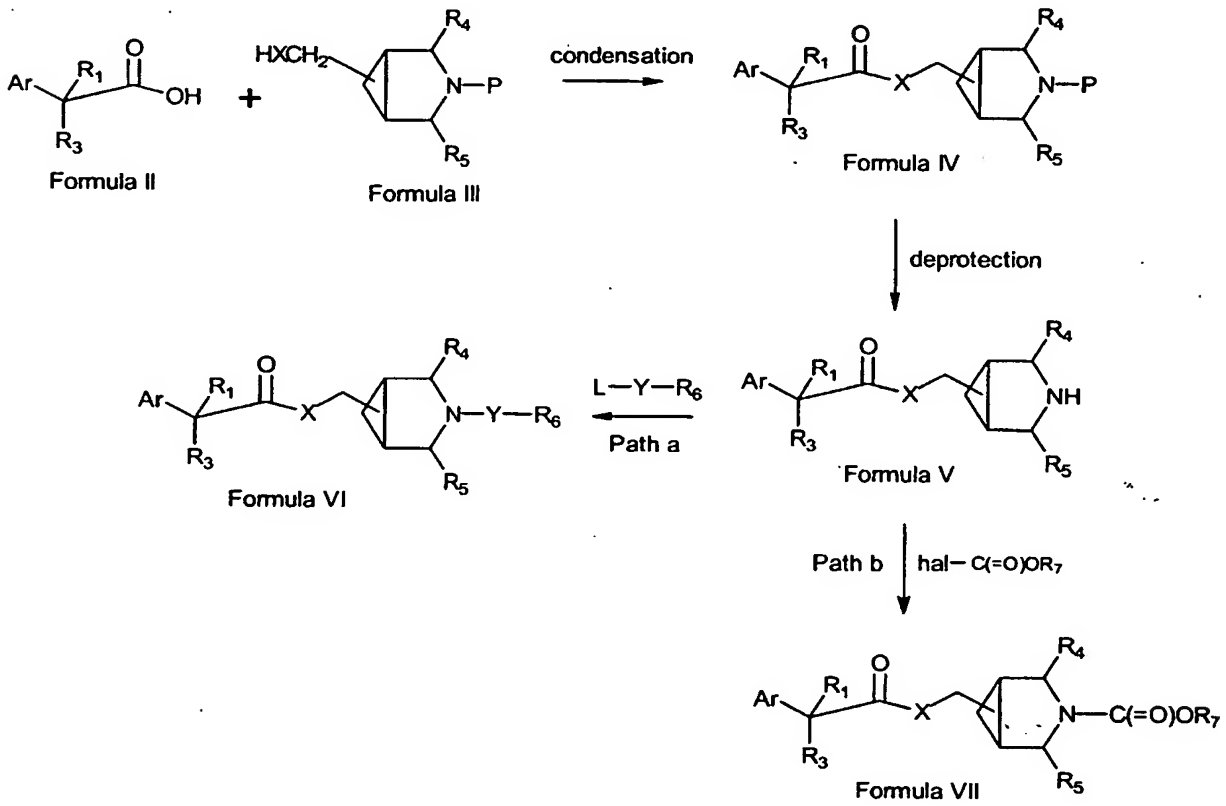
The term "protecting groups" refers to moieties that prevent chemical reaction at a location of a molecule intended to be left unaffected during chemical modification of such molecule. Unless otherwise specified, protecting groups may be used on groups, such as hydroxy, amino, or carboxy. Examples of protecting groups are found in T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", 2nd Ed., John Wiley and Sons, New York, N.Y., which is incorporated herein by reference. The species of the carboxylic protecting groups, amino protecting groups or hydroxy protecting groups employed are not critical, as long as the derivatised moieties/moiety is/are stable to conditions of subsequent reactions and can be removed without disrupting the remainder of the molecule.

The compounds of this invention contain one or more asymmetric carbon atoms and thus can occur as racemates and racemic mixtures, single enantiomers, diastereomieric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be of the R or S configuration. Although the specific compounds exemplified in this application may be depicted in a particular stereochemical configuration, compounds having either the opposite stereochemistry at any given chiral center or mixture(s) thereof are envisioned as part of the invention. Although amino acids and amino acid side chains may be depicted in a particular configuration, both natural and unnatural forms are envisioned as part of the invention.

Detailed Description of the Invention

The compounds of the present invention may be prepared by techniques well known in the art and familiar to the average synthetic organic chemist. In addition, the compounds of the present invention may be prepared by the following the reaction Schemes I, II and III

Scheme I



The compounds of Formulae VI and VII may be prepared according to Scheme I. Thus, the preparation comprises condensing a compound of Formula II (wherein Ar, R_1 and R_3 are the same as defined earlier) with a compound of Formula III (wherein X, R_4 and R_5 are the same as defined earlier and P is a protecting group for example, aralkyl or acyl) to give a compound of Formula IV, which can be deprotected to give a compound of Formula V,

Path a: the compound of Formula V is reacted with a compound of Formula L-Y-R_6 (wherein L is a leaving group for example halogen (F, Cl, Br, I), Y is –C(=O), SO_2 and R_6 is the same as defined earlier) to give a compound of Formula VI.

Path b: the compound of Formula V is reacted with a compound of Formula hal–C(=O)OR_7 (wherein R_7 is the same as defined earlier and hal is halogen (Br, Cl, I)) to give a compound of Formula VII.

The condensation of a compound of Formula II with a compound of Formula III can be carried out in the presence of a condensing agent (for example, 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride or dicyclohexylcarbodiimide in an organic base (for example, 1,8-diazabicyclo[5.4.0]undec-7-ene, N-methylmorpholine, triethylamine, diisopropylethylamine or pyridine) in an organic solvent (for example, N,N-dimethylformamide, chloroform, tetrahydrofuran, dioxane, diethylether, benzene or toluene) to give a compound of Formula IV which on deprotection (for example, hydrogenatically utilizing palladium on carbon under catalytic hydrogenation transfer conditions of ammonium formate and palladium on carbon) in an organic solvent (for example, methanol, ethanol, tetrahydrofuran and acetonitrile) gives a compound of Formula V, which on reaction with a compound of Formula L-Y-R_6 (*Path a*) in the presence of a base (for example, triethylamine, diisopropylethylamine or pyridine) in an organic solvent for example, dichloromethane, dichloroethane, chloroform or carbon tetrachloride) gives a compound of Formula VI. The reaction of a compound of Formula V (*Path b*) with a compound of Formula hal–C(=O)OR_7 can be carried out in the presence of a base (for example, triethylamine, diisopropylethylamine or pyridine) in an organic solvent (for example, dichloromethane, dichloroethane, chloroform or carbon tetrachloride) to give a compound of Formula VII.

Particular illustrative compounds which can be prepared following Scheme I include those listed below (also shown in Table I and II):

N-{[(1α, 5α, 6α)-3-(4-Nitrobenzenesulphonyl)-3-azabicyclo[3.1.0]hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 4),

N-{[(1α,5α,6α)-3-Benzenesulfonyl-3-azabicyclo[3.1.0]hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 5),

N-{[(1α,5α,6α)-3-(3,5-Dinitrobenzoyl)-3-azabicyclo[3.1.0]hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 6),

N-{[(1α,5α,6α)-3-(2-Benzyloxyacetyl)-3-azabicyclo[3.1.0]hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 7),

N-{[(1α,5α,6α)-3-Benzoyl-3-azabicyclo[3.1.0]hex-6-ylmethyl]}-2-hydroxy-2-cyclopentyl-2-phenyl acetamide (Compound No. 8),

N-{[(1α,5α,6α)-3-(3-Nitrobenzenesulphonyl)-3-azabicyclo[3.1.0]hex-6-ylmethyl]}-2-hydroxy-2-cyclopentyl-2-phenyl acetamide (Compound No. 9),

N-{[(1α,5α,6α)-3-(2-Benzo[1,3]dioxol-5-yl-acetyl)-3-azabicyclo[3.1.0]hex-6-ylmethyl]}-2-hydroxy-2-cyclopentyl-2-phenyl acetamide (Compound No. 10),

N-{[(1α,5α,6α)-3-(4-Trifluoromethylbenzenesulfonyl)-3-azabicyclo[3.1.0]hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 11),

N-{[(1α,5α,6α)-3-[2-(3,5-Difluoro-phenyl)-acetyl]-3-azabicyclo[3.1.0]hex-6-ylmethyl]}-2-hydroxy-2-cyclopentyl-2-phenyl acetamide (Compound No. 13),

N-{[(1α,5α,6α)-3-(4-Tert-butylbenzenesulfonyl)-3-azabicyclo[3.1.0]hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 14),

N-{[(1α, 5α, 6α)-3-(2-Fluorobenzoyl)-3-azabicyclo [3.1.0]hex-6-ylmethyl}]-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 15),

N-{[(1α, 5α, 6α)-3-(3,4,5-Trimethoxybenzoyl)-3-azabicyclo [3.1.0]hex-6-yl methyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 16),

N-{[(1α, 5α, 6α)-3-Phenylacetyl-3-azabicyclo [3.1.0] hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 18),

N-{[(1α, 5α, 6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid-4-nitro-benzyl ester (Compound No. 19),

N-{[(1α, 5α, 6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid isobutyl ester (Compound No. 20),

N-{[(1α, 5α, 6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 4-nitro-phenyl ester (Compound No. 21),

N-{[(1α, 5α, 6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid benzyl ester (Compound No. 22),

N-{[(1α, 5α, 6α)-3-(4-Fluorobenzenesulphonyl)-3-azabicyclo [3.1.0] hex-6-yl methyl}]-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 23)

N-{[(1α, 5α, 6α)-3-(2,4,6-Trisopropylbenzenesulphonyl)-3-azabicyclo [3.1.0] hex-6-yl methyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 24)

N-{[(1α, 5α, 6α)-3-(3,5-Dimethylbenzoyl)-3-azabicyclo [3.1.0] hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No.27)

N-{[(1α, 5α, 6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 9H-fluoren-9-ylmethyl ester (Compound No.35)

N-{[(1α, 5α, 6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid butyl ester (Compound No.36)

N-{[(1α, 5α, 6α)-3-(Methanesulphonyl)-3-azabicyclo [3.1.0] hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 37)

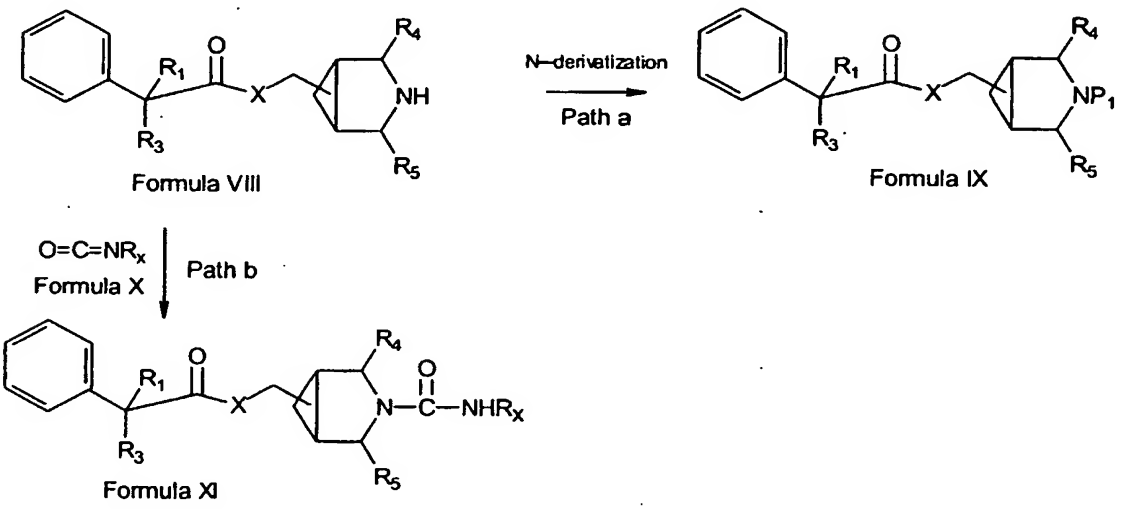
N-{[(1α, 5α, 6α)-3-(4-Methoxybenzoyl)-3-azabicyclo [3.1.0] hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 39)

N-{[(1α, 5α, 6α)-3-(3-Benzo[1,3]-dioxol-5-yl-propionyl)-3-azabicyclo [3.1.0] hex-6-yl methyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No.40)

N-{[(1α, 5α, 6α)-3-(Dimethylsulfamoyl)-3-azabicyclo [3.1.0] hex-6-yl methyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No.41)

their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, stereoisomers or polymorphs.

Scheme II



The compounds of Formulae IX and XI may be prepared according to Scheme II. Thus,

Path a: the compound of Formula VIII (wherein X, R_1, R_3, R_4 and R_5 are the same as defined earlier) undergoes N-derivatization to give a compound of Formula IX [wherein P_1 is halogen (F, Cl, Br or I), cyano or –C(=O)OR_7 (R_7 is the same as defined earlier)].

Path b: the compound of Formula VIII is reacted with a compound of Formula X (wherein R_x is the same as defined earlier) to give a compound of Formula XI.

The N-derivatization of a compound of Formula VIII *(Path a)* (when P_1 is halogen) can be carried out with halogenating agent (for example, sodium hypochlorite, sodium hypobromite or sodium hypoiodite) in an organic solvent (for example, dichloromethane, dichloroethane, chloroform or carbon tetrachloride) to give a compound of Formula IX. The N-derivatization of a compound of Formula VIII (when P_1 is cyano) can be carried out with a nitrilating agent (for example, cyanogen bromide) in the presence of an organic base (for example, triethylamine, diisopropylethylamine or pyridine) in an organic solvent

(for example, dichloromethane, dichloroethane, chloroform or carbon tetrachloride) to give a compound of Formula IX. The N-derivatization of a compound of Formula VIII (when P_1 is -C(=O)OR_7) can be carried out with anhydrides (for example, ditert-butoxycarbonyl anhydride, dipropoxycarbonyl anhydride, dimethoxycarbonyl anhydride or diethoxycarbonyl anhydride) in the presence of an organic base (for example, triethylamine, diisopropylethylamine or pyridine) in an organic solvent (for example, dichloromethane, dichloroethane, chloroform or carbon tetrachloride) to give a compound of Formula IX. The compound of Formula VIII *(Path b)* can be reacted with an isocyanate of Formula X in an organic solvent (for example, dichloroethane, dichloromethane, chloroform or carbon tetrachloride) to give a substituted urea of Formula XI.

Alternatively, the compound of Formula XI can also be prepared by reacting a compound of Formula VIII with an appropriate amine in the presence of carbonyldiimidazole (CDI) or with carbamates such as phenyl carbamate or p-nitrophenyl carbamate.

Particular representative compounds which can be prepared following Scheme II include those listed below (also listed in Table I):

N-{[(1α,5α,6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid tert-butyl ester (Compound No. 1)

N-{[(1α,5α,6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid benzylamide (Compound No.3)

N-{[(1α,5α,6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0] hexane-3-carboxylic acid (4-trifluoromethyl-phenyl)-amide (Compound No.12)

N-{[(1α,5α,6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0] hexane-3-carboxylic acid (4-fluorophenyl)-amide (Compound No.17)

N-{[(1α,5α,6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0] hexane-3-carboxylic acid allylamide (Compound No.25)

N-{[(1α,5α,6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0] hexane-3-carboxylic acid (2,4-dimethoxy-phenyl)-amide (Compound No.26)

N-{[(1α,5α,6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0] hexane-3-carboxylic acid (4-benzyloxy-phenyl)-amide (Compound No.28)

N-{[(1α,5α,6α)-3-Chloro-3-azabicyclo [3.1.0] hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 29)

N-{[(1α,5α,6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0] hexane-3-carboxylic acid amide (Compound No.30)

N-{[(1α, 5α, 6α)-3-Cyano-3-azabicyclo [3.1.0] hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 31)

N-{[(1α, 5α, 6α)-3-Chloro-3-azabicyclo [3.1.0] hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide hydrochloride salts (Compound No. 32)

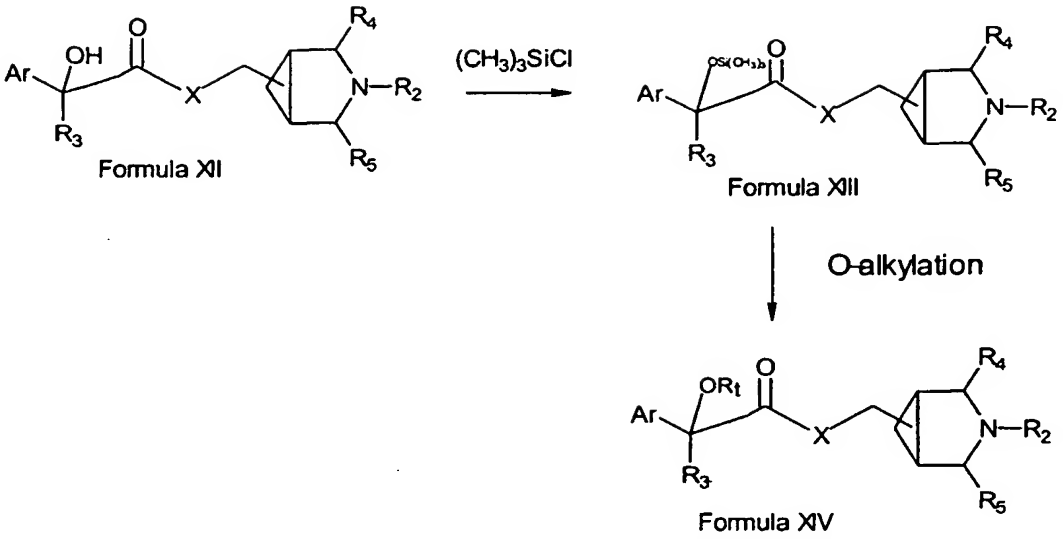
N-{[(1α, 5α, 6α)-3-Chloro-3-azabicyclo [3.1.0] hex-6-ylmethyl]}-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No. 33)

N-{[(1α, 5α, 6α)-3-Chloro-3-azabicyclo [3.1.0] hex-6-ylmethyl]}-2-hydroxy-2-diphenyl acetamide (Compound No. 34)

N-{[(1α,5α,6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0] hexane-3-carboxylic acid (2,4-difluoro-phenyl)-amide (Compound No.38)

their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, stereoisomers or polymorphs.

Scheme III



The compound of Formula XIV may be prepared by following Scheme III. The preparation comprises reacting a compound of Formula XII (where in X, R_2, R_3, R_4 and R_5 are the same as defined earlier) with trimethyl silyl chloride to give a compound of Formula XIII, which undergoes O-alkylation to give a compound of Formula XIV (wherein R_t is alkyl).

The reaction of a compound of Formula XII with trimethyl silyl chloride can be carried out in an organic base (for example, imidazole, triethylamine, N-methylmorpholine, diisopropylethylamine or pyridine) in an organic solvent (for example, dimethylformamide, tetrahydrofuran, dioxane or diethylether) to give a compound of Formula XIII which can undergo O-alkylation in the presence an organic base (for example, sodium hydride or sodium cyanoboro hydride) in an organic solvent (for example, tetrahydrofuran, dimethylformamide, diethylether or dioxane) to give a compound of Formula XIV.

Particular representative compounds which may be prepared following Scheme III include those listed below (also listed in Table I):

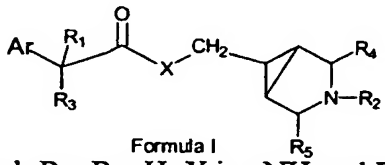
N-{[(1α, 5α, 6α)-3-Terbutyl-carboxy-3-azabicyclo [3.1.0] hex-6-ylmethyl]}-2-cyclopentyl-2-methoxy-2-phenyl acetamide (Compound No. 2)

their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, stereoisomers or polymorphs.

Also, in all the above representative examples wherever amines are specified, one skilled in an art would optionally convert them to their respective salts, for example amines can be converted to corresponding hydrochloride salts with ethanolic hydrochloric acid solution in an organic solvent selected from the group consisting of dichloromethane, dichloroethane, chloroform or carbon tetrachloride.

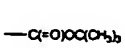
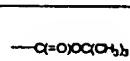
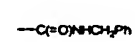
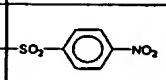
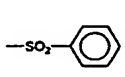
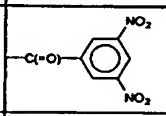
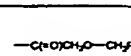
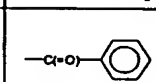
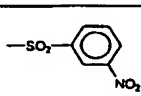
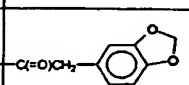
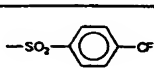
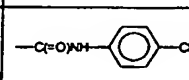
In the above schemes, where specific bases, solvents, condensing agents, etc. are mentioned, it is to be understood that other acids, bases, solvents, condensing agents, hydrolyzing agents, etc, known to those skilled in an art may also be used. Similarly the reaction temperature and duration of the reactions may be adjusted according to desired needs.

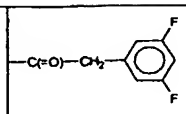
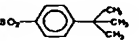
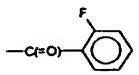
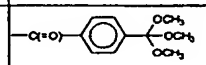
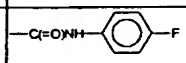
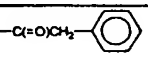
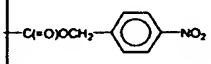
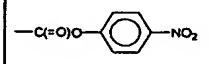
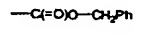
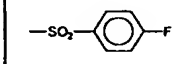
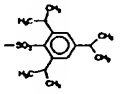
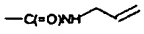
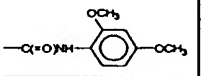
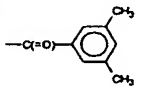
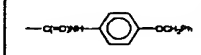
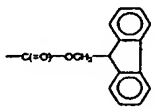
Table I



Formula I

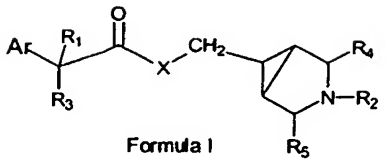
(where Ar is phenyl, R_4=R_5=H, X is –NH and R_1 is -OR_z)

Compound No.	R_z	R_2	R3	Compound No.	R_z	R_2	R3
1	H			2	-CH_3		
3	H			4	H		
5	H			6	H		
7	H			8	H		
9	H			10	H		
11	H			12	H		

13	H			14	H		
15	H			16	H		
17	H			18	H		
19	H			20	H		
21	H			22	H		
23	H			24	H		
25	H			26	H		
27	H			28	H		
29	H	-Cl		30	H	$-C(=O)NH_2$	
31	H	-CN		32 *	H	Cl	
33	H	-Cl		34	H	Cl	
35	H			36	H		
37	H	$-SO_2CH_3$		38	H		

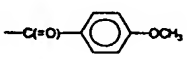
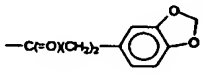
* refers to hydrochloride salt of compound No. 29.

Table II



Formula I

(where Ar is phenyl, R_4=R_5=H, X is –NH, R_1 is OR_z)

Compound No.	R_z	R_2	R3	Compound No.	R_z	R_2	R3
39	H			40	H		

Because of their valuable pharmacological properties, the compounds described herein may be administered to an animal for treatment orally, or by a parenteral route.

The pharmaceutical compositions described herein can be produced and administered in dosage units, each unit containing a certain amount of at least one compound described herein and/or at least one physiologically acceptable addition salt thereof. The dosage may be varied over extremely wide limits, as the compounds are effective at low dosage levels and relatively free of toxicity. The compounds may be administered in the low micromolar concentration, which is therapeutically effective, and the dosage may be increased as desired up to the maximum dosage tolerated by the patient.

The compounds described herein can be produced and formulated as their enantiomers, diastereomers, N-Oxides, polymorphs, solvates and pharmaceutically acceptable salts, as well as metabolites having the same type of activity. Pharmaceutical compositions comprising the molecules of Formula I or metabolites, enantiomers, diastereomers, N-oxides, polymorphs, solvates or pharmaceutically acceptable salts thereof, in combination with pharmaceutically acceptable carrier and optionally included excipient can also be produced.

EXAMPLES

Various solvents, such as acetone, methanol, pyridine, ether, tetrahydrofuran, hexanes, and dichloromethane, were dried using various drying reagents according to procedures described in literature. IR Spectra were recorded as Nujol Mulls or a thin neat

film on a Perkin Elmer Paragon instrument, Nuclear Magnetic Resonance (NMR) were recorded on Varian XL-300 MHz instument using tetramethylsilane as an internal standard.

Synthesis of (1α, 5α, 6α)-6-aminomethyl-3-benzyl-3-azabicyclo[3.1.0]hexane

This compound was synthesised following the procedure described in EP 0413455 A2.

Synthesis of 2-hydroxy-2-cyclopentyl-phenyl acetic acid

The compound was synthesised following the procedure described in Kadin *et al.*, *J. Org. Chem.*, 1962, 27, 240-245.

Synthesis of N-(1α, 5α, 6α)-(3-benzyl-3-azabicyclo[3.1.0]hex-6-ylmethyl)-2-cyclopentyl-2-hydroxy-2-phenyl-acetamide.

Step a: Synthesis of 2-hydroxy-2-cyclopentyl-2-phenyl acetic acid

This was prepared following the procedure described in *J. Amer. Chem. Soc.*, 75, 265(1953).

Step b: Synthesis of (1α, 5α, 6α)-6-aminomethyl-3-benzyl-3-azabicyclo[3.1.0]hexane.

The compound was prepared following the procedure described in EP 0 413 455 A2.

Step c: Synthesis of (1α, 5α, 6α)-N-(3-benzyl-3-azabicyclo[3.1.0]hex-6-ylmethyl)-2-cyclopentyl-2-hydroxy-2-phenyl acetamide.

To a solution of a compound obtained from step b above (29.9 mmole, 6.05 g) in dimethylformamide (100 ml) was added 2-hydroxy-2-cyclopentyl-2-phenyl acetic acid (commercially available) (27.2 mmole, 6.0 g) followed by the addition of 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide and cooled at 0°C. The reaction mixture was treated with hydroxy benzotriazole (29.9 mmole, 4.04 gm) followed by addition of N-methyl morpholine (54.4 mmole, 5.2 g) and was stirred at 0°C for 1hour and at room temperature overnight. The reaction mixture was poured into saturated sodium bicarbonate solution. The organic compound was extracted with ethyl acetate. The organic layers were washed with water and dried over anhydrous sodium sulphate and

concentrated under reduced pressure. The residue was purified by column chromatography to yield the title compound with 95% yield.

The analogs of (1α, 5α, 6α)-N-(3-benzyl-3-azabicyclo[3.1.0]hex-6-ylmethyl)-2-cyclopentyl-2-hydroxy-2-phenyl-acetamide described below, can be prepared by replacing appropriate acid in place of 2-hydroxy 2-cyclopentyl phenyl acetic acid.

N-(1α, 5α, 6α)-(3-Benzyl-3-azabicyclo[3.1.0]hex-6-ylmethyl)-2-cyclobutyl-2-hydroxy-2-phenyl acetamide

N-(1α, 5α, 6α)-(3-Benzyl-3-azabicyclo[3.1.0]hex-6-ylmethyl)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide

N-(1α, 5α, 6α)-(3-Benzyl-3-azabicyclo[3.1.0]hex-6-ylmethyl)-2-hydroxy-2,2-phenyl acetamide

Synthesis of N-(1α, 5α, 6α)-(3-azabicyclo[3.1.0]hex-6-ylmethyl)-2-cyclopentyl-2-hydroxy-2-phenyl acetamide.

To a solution of N-(1α, 5α, 6α)-(3-benzyl-3-azabicyclo[3.1.0]hex-6-ylmethyl)-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (1.0 g, 2.48 mmole) in dry methanol (25.0 ml), was added palladium on carbon (5%, 0.2 g) under N_2 atmosphere followed by the addition of ammonium formate (0.8 g, 12.38 mmole) under constant stirring. The reaction mixture was refluxed for half an hour under N_2 atmosphere. The reaction mixture was cooled to room temperature and the reaction mixture was filtered through hyflo bed. The hyflo bed was washed with methanol (75.0 ml), ethyl acetate (25.0 ml) and water (25.0 ml). The filtrate was concentrated under vacuum. The residue thus obtained was diluted with water and pH of the resulting solution was adjusted to pH~14 with sodium hydroxide. The compound was extracted with ethyl acetate (2×50 ml) and the ethyl acetate layer was washed with water and brine solution. The layer was dried over anhydrous sodium sulphate and concentrated to give the title compound with 96.2% yield.

The analogs of N-(1α, 5α, 6α)-(3-azabicyclo[3.1.0]hex-6-ylmethyl)-2-cyclopentyl-2-hydroxy-2-phenyl acetamide described below, can be prepared by deprotection of appropriate amine, as applicable in each case.

N-(1α, 5α, 6α)-(3-Azabicyclo[3.1.0]hex-6-ylmethyl)-2-cyclobutyl-2-hydroxy-2-phenyl acetamide

N-(1α, 5α, 6α)-(3-Azabicyclo[3.1.0]hex-6-ylmethyl)-2-cyclohexyl-2-hydroxy-2-phenyl acetamide

N-(1α, 5α, 6α)- (3-Azabicyclo[3.1.0]hex-6-ylmethyl)-2-hydroxy-2,2-diphenyl acetamide

SCHEME I, PATH *A* PROCEDURE

Example 1: Synthesis of N-{[(1α, 5α, 6α)-3-(4-nitrobenzenesulphonyl)-3-azabicyclo[3.1.0]hex-6-yl methyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 4)

To a solution of N-(1α, 5α, 6α)-(3-azabicyclo[3.1.0]hex-6-ylmethyl)-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (0.796 mmole) and triethyl amine (1.592 mmol) in dichloromethane (10.0 ml) at 0°C was added p-nitro phenyl sulphonyl chloride (0.955 mmole). The reaction mixture was stirred for 1 hour at 0°C and then at room temperature for overnight. The solid thus separated was filtered, washed thoroughly with dichloromethane and dried to get the title compound with 60% yield; M.P: 225.3-227.1°C; IR (KBr): 1642.5 cm^{-1}; ^1H NMR (DMSO-d_6):δ 8.39-8.42 (m, 2H), 7.91-7.99 (m, 2H), 7.54-7.56 (m, 2H), 7.22-7.32 (m, 3H), 5.47 (s, 1H), 3.06-3.09 (m, 3H), 2.90-2.92 (m, 2H), 2.76-2.79 (m, 2H), 1.42-1.47 (m, 9H), 1.25-1.28 (m, 2H), 0.61 (brs, 1H); Mass (m/z): 500 (M^++1), 482 (M^+-OH).

Analogs of N-{[(1α, 5α, 6α)-3-(4-nitrobenzenesulphonyl)-3-azabicyclo[3.1.0]hex-6-yl methyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 4) described below, can be prepared by replacing appropriate sulfonyl group in place of n-nitro phenyl sulfonyl chloride, as applicable in each case.

N-{[(1α, 5α, 6α)-3-Benzenesulfonyl-3-azabicyclo[3.1.0]hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 5)

N-{[(1α,5α,6α)-3-(3-Nitrobenzenesulphonyl)-3-azabicyclo[3.1.0]hex-6-ylmethyl]}-2-hydroxy-2-cyclopentyl-2-phenyl acetamide (Compound No. 9)

N-{[(1α,5α,6α)-3-(4-Trifluoromethylbenzenesulfonyl)-3-azabicyclo[3.1.0]-hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 11)

N-{[(1α,5α,6α)-3-(4-Tert-butylbenzenesulfonyl)-3-azabicyclo[3.1.0]-hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 14)

N-{[(1α, 5α, 6α)-3-(4-Fluorobenzenesulphonyl)-3-azabicyclo [3.1.0] hex-6-ylmethyl]} {-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 23)

N-{[(1α, 5α, 6α)-3-(2,4,6-Trisopropylbenzenesulfonyl)-3-azabicyclo [3.1.0] hex-6-yl methyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 24)

N-{[(1α, 5α, 6α)-3-(Methanesulfonyl)-3-azabicyclo [3.1.0] hex-6-yl methyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 37)

N-{[(1α, 5α, 6α)-3-(Dimethylsulfamoyl)-3-azabicyclo [3.1.0] hex-6-yl methyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No.41)

Example 2: Synthesis of N-{[(1α,5α,6α)-3-[2-(3,5-difluorophenyl)-acetyl]-3-azabicyclo (3.1.0)-hex-6-ylmethyl}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 13)

The compound was prepared following the procedure as described for the synthesis of Compound No. 4, Example-1 by using 2,4-difluoro phenyl acetyl chloride in place of p-nitro phenyl sulphonyl chloride with 54% yield; IR (KBr): 1640.9 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.59-7.61 (m, 2H), 7.19-7.37 (m, 4H), 6.76-6.86 (m, 2H), 6.65 (brs, 1H), 3.73-3.77 (m, 1H), 3.40-3.51 (m, 4H, including –OH), 3.22-3.23 (m, 7H).

Analogs of N-{[(1α,5α,6α)-3-[2-(3,5-difluorophenyl)-acetyl]-3-azabicyclo-(3.1.0)-hex-6-ylmethyl}-2-hydroxy-2-phenyl acetamide (Compound No. 13) described below, can be prepared by replacing appropriate acyl halide group in place of 2,4-difluoro phenyl acetyl chloride, as applicable in each case.

N-{[(1α,5α,6α)-3-(3,5-Dinitrobenzoyl)-3-azabicyclo[3.1.0]hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 6),

N-{[(1α,5α,6α)-3-(2-Benzyloxyacetyl)-3-azabicyclo[3.1.0]hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 7),

N-{[(1α,5α,6α)-3-Benzoyl-3-azabicyclo[3.1.0]hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 8),

N-{[(1α,5α,6α)-3-(2-Benzo[1,3]dioxol-5-yl-acetyl)-3-azabicyclo[3.1.0]hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 10),

N-{[(1α, 5α, 6α)-3-(2-Fluorobenzoyl)-3-azabicyclo [3.1.0] hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 15),

N-{[(1α, 5α, 6α)-3-(3,4,5-Trimethoxybenzoyl)-3-azabicyclo [3.1.0] hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 16),

N-{[(1α, 5α, 6α)-3-Phenylacetyl-3-azabicyclo [3.1.0] hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 18),

N-{[(1α, 5α, 6α)-3-(3,5-Dimethylbenzoyl)-3-azabicyclo [3.1.0] hex-6-ylmethyl]-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No.27).

Example 3:Synthesis of N-{[(1α, 5α, 6α)-3-(4-methoxy-benzoyl)-3-azabicyclo [3.1.0] hex-6-yl methyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 39)

The compound was synthesised following the procedure as described for the synthesis of compound No. 4, Example-1 by using 4-methoxy benzoyl chloride in place of p-nitro benzene sulfonyl chloride with 90% yield; M.P: 58.3-59.6°C; IR (KBr): 1656.3, 1610.3 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.57-7.60 (m, 2H), 7.21-7.41 (m, 5H), 6.87-6.90 (m, 2H), 3.83 (s, 3H), 3.40-3.59 (m, 3H), 3.03-3.10 (m, 4H), 1.42-1.65 (m, 9H), 1.26-1.40 (m, 2H), 0.72-0.74 (m, 1H); Mass (m/z): 449 (M^++1), 431 (M^+-OH)

Analogs of N-{[(1α, 5α, 6α)-3-(4-methoxybenzoyl)-3-azabicyclo [3.1.0] hex-6-yl methyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 39) described

below, can be prepared by replacing appropriate acyl halide group in place of 4-methoxy benzoyl chloride as applicable in each case.

N-{[(1α, 5α, 6α)-3-(3-Benzo[1,3]-dioxol-5-yl-propionyl)-3-azabicyclo [3.1.0] hex-6-yl methyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No.40),

SCHEME I, PATH B PROCEDURE

Example 4: Synthesis N-{[(1α, 5α, 6α)-6-[(2-cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 4-nitro-benzyl ester (Compound No.19)

The title compound was prepared following the procedure described for the synthesis of Compound No. 4, Example-1 by using 4-nitrobenzyl chloroformate in place of 4-methoxy benzoyl chloride with 46% yield; M.P: 73.1-74.3°C; IR (KBr): 1635.0 cm^{-1}; ^1H NMR ($CDCl_3$):δ 7.59-7.62 (m, 2H), 7.29-7.37 (m, 4H), 6.63-6.74 (m, 2H), 6.59 (brs, 1H), 5.91 (s, 2H), 3.72-3.76 (m, 1H), 3.02-3.37 (m, 6H, including –OH), 2.85 (t, 2H, J=6Hz), 2.42 (t, 2H, J=6Hz), 1.26-1.66 (m, 11H), 0.75 (m, 1H); Mass (m/z): 491 (M^++1), 473 (M^+-OH).

Analogs of N-{[(1α, 5α, 6α)-6-[(2-cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 4-nitro-benzyl ester (Compound no.19) described below, can be prepared by replacing appropriate chloroformate in place of 4-nitro benzyl chloroformate, as applicable in each case.

N-{[(1α, 5α, 6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid isobutyl ester (Compound No. 20),

N-{[(1α, 5α, 6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 4-nitro-phenyl ester (Compound No. 21),

N-{[(1α, 5α, 6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid benzyl ester (Compound No. 22),

N-{[(1α, 5α, 6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 9H-fluoren-9-ylmethyl ester (Compound No.35),

N-{[(1α, 5α, 6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid butyl ester (Compound No.36),

SCHEME II, PATH *A* PROCEDURE

Example 5: Synthesis of N-{[(1α, 5α, 6α)-3-chloro-3-azabicyclo [3.1.0] hex-6-yl methyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 29)

To a solution of N-(1α, 5α, 6α)-(3-azabicyclo[3.1.0]hex-6-ylmethyl)-2-cyclopentyl-2-hydroxy-2-phenyl acetamide in dichloromethane (10.0 ml), was added sodium hypochlorite (4.0 ml) at room temperature and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with chloroform and water followed by stirring it for five minutes. The organic layer was separated, washed thoroughly with water, dried and concentrated to get the title organic compound with 90% yield; M.P: 130.7-131.9°C; IR (KBr): 1656.8 cm^{-1}; ^1H NMR ($CDCl_3$):δ 7.59-7.61 (m, 2H), 7.30-7.38 (m, 3H), 3.61-3.68 (m, 2H), 3.03-3.17 (m, 4H), 1.49-1.69 (m, 9H), 1.11-1.26 (m, 2H), 0.83 (s, 1H); Mass (m/z): 349 (M^++1), 331 (M^+-OH).

Analogs of N-{[(1α, 5α, 6α)-3-chloro-3-azabicyclo[3.1.0]hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 29) described below, can be prepared by replacing appropriate amine in place of (1α, 5α, 6α)-N-(3-azabicyclo[3.1.0]hex-6-ylmethyl)-2-cyclopentyl-2-hydroxy-2-phenyl-acetamide, as applicable in each case.

N-{[(1α, 5α, 6α)-3-Chloro-3-azabicyclo [3.1.0] hex-6-ylmethyl]}-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No. 33),

N-{[(1α, 5α, 6α)-3-Chloro-3-azabicyclo [3.1.0] hex-6-ylmethyl]}-2-hydroxy-2-diphenyl acetamide (Compound No. 34).

Example 6: Synthesis of hydrochloride salt of N-{[(1α, 5α, 6α)-3-chloro-3-azabicyclo [3.1.0] hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide hydrochloride salt (Compound No. 32)

To a solution of the compound No. 29 (0.15 g) in dichloromethane (5.0 ml), was added ethanolic hydrochloric acid solution (3N, 0.5 ml) and stirred the reaction mixture for 10 minutes. The solvent was evaporated off under reduced pressure and the residue thus obtained was triturated with diethylether to get the solid. The solid was dried under vacuum to furnish the title compound with 90% yield; ^{1}H NMR (DMSO-d_6): 8.02 (t, 1H, J=6Hz), 7.56-7.59 (m, 2H), 7.19-7.32 (m, 3H), 5.55 (s, 1H), 2.98-3.16 (m, 4H, including –OH), 2.85-2.94 (m, 3H), 1.24-1.53 (m, 11H), 1.07 (t, 1H, J=3Hz).

Example 7: Synthesis of N-{[(1α, 5α, 6α)-3-cyano-3-azabicyclo [3.1.0] hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 31)

To a solution of N-(1α, 5α, 6α)-(3-azabicyclo[3.1.0]hex-1-ylmethyl)-2-cyclopentyl-2-hydorxy-2-phenyl acetamide (0.25 g) and triethylamine (0.22 ml) in dichloromethane (5.0 ml) at room temperature, was added cyanogen bromide (0.25 g) and the reaction mixture was stirred at the same temperature for half on hour. The reaction mixture was cooled to 0°C followed by the addition of sodium hydroxide (0.5 N) and stirred for 10 minutes. Organic layer was separated, washed with brine solution, dried and concentrated under reduced pressure. The residue was purified by column chromatography using ethylacetate in hexane solvent mixture as an eluent to furnish the title organic compound with 74% yield; M.P: 122.6-123.8°C; IR (KBr): 2213.5, 1648.4 cm^{-1}; ^{1}H NMR ($CDCl_3$):δ 7.59-7.61 (m, 2H), 7.30-7.38 (m, 3H), 6.65 (brs,1H), 3.32-3.47 (m, 4H, including –OH), 3.09-3.22 (m, 3H), 1.19-1.57 (m, 11H), 0.91 (brs, 1H); Mass (m/z): 340 (M^++OH), 322 (M^+-OH).

Example 8: Synthesis of N-{[(1α,5α,6α)-6-{[(2-cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid tert-butyl ester (Compound No. 1)

To a cold solution of N-(1α, 5α, 6α)-(3-azabicyclo[3.1.0]hex-1-ylmethyl)-2-cyclopentyl-2-hydroxy acetamide (5.1 mmole) in dichloromethane, was added triethylamine (10.1 mmole) followed by the addition of di-tertbutoxy carbonyl anhydride (6.1 mmole). The reaction mixture was stirred at same temperature for 30 minutes and then at room temperature for 3½ hour. The organic layer was separated and the aqueous

layer was extracted with dichloromethane. The combined organic layer was dried over anhydrous sodium sulphate and concentrated. The crude organic compound was purified by column chromatography using ethyl acetate in hexane solvent mixture as eluent to furnish the title compound with 75% yield; ^{1}H NMR ($CDCl_3$): δ 7.61-7.59 (2H, m), 7.37-7.28 (3H, m), 6.55 (1H, brs), 3.48-3.45 (2H, m), 3.29-3.26 (2H, m), 3.08-3.03 (3H, m), 1.69-1.55 (8H, m), 1.42-1.36 (9H, m), 1.23-1.18 (2H, m), 0.74-0.72 (1H, m); Mass (m/z): 414 (M^++1).

SCHEME II, PATH B PROCEDURE

Example 9: Synthesis of N-{[(1α,5α,6α)-6-{[(2-cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid benzylamide (Compound No.3)

To a solution of N-(1α, 5α, 6α)-(3-azabicyclo[3.1.0]hex-1-ylmethyl)-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (0.8 mmole) in dichloroethane (100 ml), was added benzyl isocyanate (0.955 mmole) at room temperature and stirred for 1 hour at the same temperature. The reaction mixture was directly absorbed onto the silica gel and purified by column chromatography using methanol in chloroform as an eluent with 85% yield; m.p: 76-78°C; IR (KBr): 1636.4, 1527.7 cm^{-1}; ^{1}H NMR ($CDCl_3$):δ 7.58-7.61 (m, 2H), 7.23-7.36 (m, 8H), 6.62 (brs, 1H), 4.39 (s, 2H), 3.33-3.47 (m, 4H), 3.06-3.16 (m, 4H), 1.45-1.70 (m, 9H), 1.25 (brs, 2H), 0.79 (t, 1H, J=6Hz); Mass (m/z): 448 (M^++1), 430 (M^+-OH).

The analogs of N-{[(1α,5α,6α)-6-{[(2-cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid benzylamide (Compound No.3) described below, can be prepared by replacing appropriate isocyanate in place of benzyl isocyanate, as applicable in each case.

N-{[(1α,5α,6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]-3-aza-bicyclo[3.1.0] hexane-3-carboxylic acid-(4-trifluoromethyl-phenyl)-amide (Compound No.12)

N-{[(1α,5α,6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0] hexane-3-carboxylic acid-(4-fluoro-phenyl)-amide (Compound No.17)

N-{[(1α,5α,6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0] hexane-3-carboxylic acid allylamide (Compound No.25)

N-{[(1α,5α,6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0] hexane-3-carboxylic acid-(2,4-dimethoxy-phenyl)-amide (Compound No.26)

N-{[(1α,5α,6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0] hexane-3-carboxylic acid-(4-benzyloxy-phenyl)-amide (Compound No.28)

N-{[(1α,5α,6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0] hexane-3-carboxylic acid amide (Compound No.30)

N-{[(1α,5α,6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0] hexane-3-carboxylic acid-(2,4-difluoro-phenyl)-amide (Compound No.38)

SCHEME III PROCEDURE

Example 10: Synthesis of *N*-{[(1α, 5α, 6α)-3-terbutyl-carboxy-3-azabicyclo [3.1.0] hex-6-yl methyl]}-2-cyclopentyl-2-methoxy-2-phenyl acetamide (Compound No. 2)

Step a: Synthesis of 4-[(2-cyclopentyl-2-hydroxy-2-phenyl acetamide)-methyl]-3-methyl piperidine-1-carboxylic acid tert-butyl ester

To a solution of (1α, 5α, 6α)-N-(3-azabicyclo[3.1.0]hex-1-ylmethyl)-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (0.3 g, 1 mmole) in dichloromethane was added trimethyl amine at 0°C followed by the addition of ditert-butoxy carboxyl anhydride (0.261 g, 1.2 mmole) in dichloromethane. Reaction mixture was stirred at 0°C for 30 minutes then at room temperature for 3½ hours. The reaction mixture was poured into water and the layers were separated. The aqueous layer was extracted with dichloromethane. The combined organic layer was dried over anhydrous was purified by column chromatography to give the title compound.

Step b: Synthesis of 4-[(2-cyclopentyl-2-phenyl-2-trimethylaryloxy-acetylamino)-methyl]-3-methyl-piperidine-1-carboxylic acid tert-butyl ester

To a solution of a compound obtained form step a above (0.414 g, 1 mmole) in dimethylformamide, was added imidazole (0.251 g, 3.7 mmole) followed by the addition of trimethyl silyl chloride (0.293 g, 2.7 mmole) at room temperature and stirred at same temperature for 2 hours. Reaction mixture was poured into water and extracted with diethylether. The organic layer was separated, dried over anhydrous sodium sulphate and concentrated under reduced pressure crude organic compound was purified by column chromatography.

Step c: Synthesis of N-{[(1α, 5α, 6α)-3-terbutyl-carboxy-3-azabicyclo [3.1.0] hex-6-yl methyl]}-2-cyclopentyl-2-methoxy-2-phenyl acetamide (Compound No. 2)

To a solution of a compound obtained from step b above (0.486 g, 1 mmole) in dry tetrahydrofuran at 0°C, was added sodium hydride (0.080 g, 2 mmole, 60% suspension in mineral oil) followed by the addition of tetra n-butyl ammonium iodide (0.025 g, 0.07 mmole). The reaction mixture was stirred at same temperature for 30 minutes and then at room temperature for 1 hour followed by cooling the reaction mixture at 0°C.

To the reaction mixture iodomethane (1.28 g, 9 mmole) was added. The reaction mixture was allowed to warm at room temperature and then stirred overnight. The reaction mixture was quenched with ammonium chloride solution and the organic compound was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude organic compound was purified by column chromatography to furnish the title compound with 34% yield; iR (KBr): 1657.8 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.26-7.46 (m, 5Ar –H), 6.99 (s, 1H), 3.17-3.25 (m, 2H), 3.15 (s, 3H), 2.87-3.00 (m, 6H), 1.67-1.85 (m, 8H), 0.86-0.88 (m, 2H); Mass (m/z): 428 (M^++1).

Biological Activity

Radioligand Binding Assays:

The affinity of test compounds for M_2 and M_3 muscarinic receptor subtypes was determined by [^{3}H]-N-methylscopolamine binding studies using rat heart and submandibular gland respectively as described by Moriya et al., (Life Sci, 1999,64(25):2351-2358) with minor modifications. In competition binding studies, specific binding of [3H] NMS was also determined using membranes from Chinese hamster ovary (CHO) cells expressing cloned human M_1, M_2, M_3, M_4 and M_5 receptors. Selectivities were calculated from the Ki values obtained on these human cloned membranes.

Membrane preparation: Submandibular glands and heart were isolated and placed in ice cold homogenising buffer (HEPES 20mM, 10mM EDTA, pH 7.4) immediately after sacrifice. The tissues were homogenised in 10 volumes of homogenising buffer and the homogenate was filtered through two layers of wet gauze and filtrate was centrifuged at 500g for 10min. The supernatant was subsequently centrifuged at 40,000g for 20 min. The pellet thus obtained was resuspended in assay buffer (HEPES 20 mM, EDTA 5mM, pH 7.4) and were stored at -70^{o}C until the time of assay.

Ligand binding assay: The compounds were dissolved and diluted in DMSO. The membrane homogenates (150-250 µg protein) were incubated in 250 µl of assay volume (HEPES 20 mM, pH 7.4) at 24-25^{o}C for 3h. Non-specific binding was determined in the presence of 1 µM atropine. The incubation was terminated by vacuum filtration over GF/B fiber filters (Wallac). The filters were then washed with ice-cold 50mM Tris HCl buffer (pH 7.4). The filter mats were dried and bound radioactivity retained on filters was counted. The IC_{50} & Kd were estimated by using the non-linear curve-fitting program using G Pad Prism software. The value of inhibition constant Ki was calculated from competitive binding studies by using Cheng & Prusoff equation *(Biochem Pharmacol, 1973,22: 3099-3108)*, $Ki = IC_{50} /(1+L/Kd)$, where L is the concentration of [^{3}H]NMS used in the particular experiment. pki is –log [Ki].

Functional Experiments using isolated rat bladder: Methodology:

Animals were euthanized by overdose of thiopentone and whole bladder was isolated and removed rapidly and placed in ice cold Tyrode buffer with the following composition (mMol/L) NaCl 137; KCl 2.7; $CaCl_2$ 1.8; $MgCl_2$ 0.1; $NaHCO_3$ 11.9; NaH_2PO_4 0.4; Glucose 5.55 and continuously gassed with 95% O_2 and 5 % CO_2.

The bladder was cut into longitudinal strips (3mm wide and 5-6 mm long) and mounted in 10 ml organ baths at 30° C, with one end connected to the base of the tissue holder and the other end connected through a force displacement transducer. Each tissue was maintained at a constant basal tension of 1 g and allowed to equilibrate for $1^{1/2}$ hour during which the Tyrode buffer was changed every 15-20 min. At the end of equilibration period the stabilization of the tissue contractile response was assessed with 1µmol/L of Carbachol till a reproducible response is obtained. Subsequently a cumulative concentration response curve to carbachol (10^{-9} mol/L to 3 X 10^{-4} mol/L) was obtained. After several washes, once the baseline was achieved, cumulative concentration response curve was obtained in presence of NCE (NCE added 20 min. prior to the second cumulative response curve.

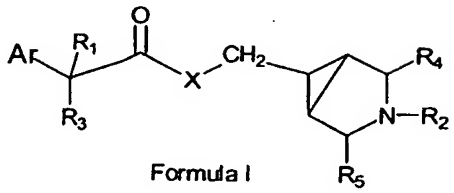
The contractile results were expressed as % of control E max. ED_{50} values were calculated by fitting a non-linear regression curve (Graph Pad Prism). pK_b values were calculated by the formula pK_b = - log [(molar concentration of antagonist/ (dose ratio-1))] where, dose ratio = ED_{50} in the presence of antagonist/ED_{50} in the absence of antagonist. The results of in-vitro tests are found to be ≤ 10.

The particular compounds specified herein exhibited K_i values for M_2 receptors of from about 10,000 nM to about 7.8 nM, for example from about 1000 nM to about 7.8 nM, or from about 60 nM to about 7.8 nM, or from about 9.0 to about 7.8 nM. The particular compounds specified herein exhibited K_i values for M_3 receptors of from about 1000 nM to about 0.5 nM, for example from about 500 nM to about 0.5 nM, or from about 30 nM to about 0.5 nM, or from about 0.7 to about 0.5 nM.

While the present invention has been described in terms of its specific embodiments, certain modification and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

We Claim:

1. Compounds having the structure of Formula I



Formula I

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, stereoisomers or polymorphs, wherein

R_1 is hydrogen, lower (C_1-C_6) alkyl, lower (C_2-C_7) alkenyl, lower (C_2-C_7) alkynyl, cycloalkyl, amino, substituted amino, -OR_z {wherein R_z is selected from hydrogen, -$Si(CH_3)_3$, lower (C_1-C_6) alkyl, lower (C_2-C_6) alkenyl, lower (C_2-C_6) alkynyl, cycloalkyl, aryl, and -$C(=O)NHR_r$ (wherein R_r is selected from hydrogen, lower (C_1-C_6) alkyl, lower (C_2-C_6) alkenyl, lower (C_2-C_6) alkynyl, aryl, and cycloalkyl)};

R_2 is carboxy, -SO_2R_6 {wherein R_6 is selected from alkyl, alkenyl, alkynyl, cycloalkyl, -NR_pR_q (wherein R_p and R_q are selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, and heteroarylalkyl), aryl, aralkyl, heteroaryl, heterocyclyl, heterocyclylalkyl, and heteroarylalkyl, or R_p and R_q may also together join to form a heterocyclyl ring}, -$C(=O)OR_7$ (wherein R_7 is selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and aralkyl), -$C(=O)NR_xR_y$ (wherein R_x and R_y are each independently selected from hydrogen, hydroxy (as restricted by the definition that both R_x and R_y cannot be hydroxy at the same time), alkyl, alkenyl, alkynyl, aryl, aralkyl, $S(O)_2R_6$ wherein R_6 is the same as defined above, heteroaryl, heterocyclyl, heteroarylalkyl, and heterocyclylalkyl, or R_x and R_y may also together join to form a heterocyclyl ring), acyl, halogen (F, Cl, Br, I), cyano, -NR_xR_y, wherein R_x and R_y are the same as defined above), or -$C(=O)CH_2OR_x$ (wherein R_x is the same as defined above);

R_3 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, and heteroarylalkyl;

R_4 and R_5 are independently selected from hydrogen, lower (C_1-C_6) alkyl, lower (C_2-C_7) alkenyl, and lower (C_2-C_7) alkynyl;

X is oxygen, -NR_7 (wherein R_7 is selected from hydrogen, lower (C_1-C_6) alkyl, lower (C_2-C_7) alkenyl, lower (C_2-C_7) alkynyl, aralkyl, and aryl; and

Ar is aryl, heteroaryl, and heterocyclyl.

2. A compound according to claim 1, wherein Ar is aryl, heteroaryl or heterocyclyl.

3. A compound according to claim 1, wherein Ar is aryl.

4. A compound according to claim 1, wherein Ar is phenyl.

5. A compound according to claim 1, wherein R_1 is $-OR_z$.

6. A compound according to claim 1, wherein R_1 is $-OR_z$ and R_z is hydrogen, alkyl, alkenyl or alkynyl.

7. A compound according to claim 1, wherein R_1 is $-OR_z$ and R_z is hydrogen.

8. A compound according to claim 1, wherein R_1 is $-OR_z$ and R_z is alkyl.

9. A compound according to claim 1, wherein R_1 is $-OR_z$ and R_z is methyl.

10. A compound according to claim 1, wherein R_2 is $-COOR_7$, $-C(=O)NR_xR_y$, SO_2R_6, $-C(=O)CH_2OR_x$, acyl, halogen or cyano.

11. A compound according to claim 1, wherein R_2 is $-COOR_7$.

12. A compound according to claim 1, wherein R_2 is $-COOR_7$ wherein R_7 is optionally substituted alkyl, optionally substituted aryl or optionally substituted aralkyl.

13. A compound according to claim 12, wherein R_7 is tert-butyl, isobutyl, fluorinemethyl, isopropyl or butyl.

14. A compound according to claim 12, wherein R_7 is nitrophenylmethyl, nitrophenyl or benzyl.

15. A compound according to claim 1, wherein R_2 is $-C(=O)NR_xR_y$.

16. A compound according to claim 15, wherein R_x is hydrogen and R_y is hydrogen, alkenyl, optionally substituted aralkyl, optionally substituted aryl.

17. A compound according to claim 16, wherein R_y is hydrogen.

18. A compound according to claim 16, wherein R_y is alkenyl.

19. A compound according to claim 16, wherein R_y is benzyl.

20. A compound according to claim 16, wherein R_y is fluorophenyl, trifluoromethylphenyl, difluorophenyl, dimethoxyphenyl or benzyloxyphenyl.

21. A compound according to claim 1, wherein R_2 is SO_2R_6.

22. A compound according to claim 21, wherein R_6 is optionally substituted aryl, alkyl or NR_pR_q.

23. A compound according to claim 22, wherein R_6 is phenyl, nitrophenyl, trifluoromethylphenyl, tert-butylphenyl, fluorophenyl, phenyl or tri-isopropyl.

24. A compound according to claim 22, wherein R_6 is methyl.

25. A compound according to claim 22, wherein R_6 is $-NR_pR_q$.

26. A compound according to claim 25, wherein wherein R_p and R_q are alkyl.

27. A compound according to claim 26, wherein R_p and R_q are methyl.

28. A compound according to claim 1, wherein R_2 is $-C(=O)CH_2OR_x$.

29. A compound according to claim 28, wherein R_x is aralkyl.

30. A compound according to claim 29, wherein R_x is benzyl.

31. A compound according to claim 1, wherein R_2 is cyano.

32. A compound according to claim 1, wherein R_2 is halogen.

33. A compound according to claim 32, wherein R_2 is chlorine.

34. A compound according to claim 1, wherein R_2 is acyl.

35. A compound according to claim 34, wherein R_2 is benzylcarbonyl, trimethoxymethylbenzoyl, difluorobenzylcarbonyl, benzodioxolmethylcarbonyl, fluorobenzoyl, benzoyl or dinitrobenzoyl.

36. A compound according to claim 1, wherein R_3 is cycloalkyl or aryl.

37. A compound according to claim 36, wherein R_3 is cycloalkyl.

38. A compound according to claim 37, wherein R_3 is cyclopentyl.

39. A compound according to claim 36, wherein R_3 is aryl.

40. A compound according to claim 39, wherein R_3 is phenyl.

41. A compound according to claim 1, wherein R_4 is hydrogen, alkyl, alkenyl or alkynyl.

42. A compound according to claim 41, wherein R_4 is hydrogen.

43. A compound according to claim 1, wherein R_5 is hydrogen, alkyl, alkenyl or alkynyl.

44. A compound according to claim 43, wherein R_5 is hydrogen.

45. A compound according to claim 1, wherein X is oxygen or –NR.

46. A compound according to claim 45, wherein X is oxygen.

47. A compound selected from

N-{[(1α, 5α, 6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid tert-butyl ester (Compound No. 1),

N-{[(1α, 5α, 6α)-3-Terbutyl-carboxy-3-azabicyclo [3.1.0] hex-6-ylmethyl]}-2-cyclopentyl-2-methoxy-2-phenyl acetamide (Compound No. 2),

N-{[(1α, 5α, 6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid benzylamide (Compound No.3),

N-{[(1α, 5α, 6α)-3-(4-Nitrobenzenesulphonyl)-3-azabicyclo[3.1.0]hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 4),

N-{[(1α, 5α, 6α)-3-Benzenesulfonyl-3-azabicyclo[3.1.0]hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 5),

N-{[(1α,5α,6α)-3-(3,5-Dinitrobenzoyl)-3-azabicyclo[3.1.0]hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 6),

N-{[(1α,5α,6α)-3-(2-Benzyloxyacetyl)-3-azabicyclo[3.1.0]hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 7),

N-{[(1α,5α,6α)-3-Benzoyl-3-azabicyclo[3.1.0]hex-6-ylmethyl]}-2-hydroxy-2-cyclopentyl-2-phenyl acetamide (Compound No. 8),

N-{[(1α,5α,6α)-3-(3-Nitrobenzenesulphonyl)-3-azabicyclo[3.1.0]hex-6-ylmethyl]}-2-hydroxy-2-cyclopentyl-2-phenyl acetamide (Compound No. 9),

N-{[(1α,5α,6α)-3-(2-Benzo[1,3]dioxol-5-yl-acetyl)-3-azabicyclo[3.1.0]hex-6-ylmethyl]}-2-hydroxy-2-cyclopentyl-2-phenyl acetamide (Compound No. 10),

N-{[(1α,5α,6α)-3-(4-Trifluoromethylbenzenesulfonyl)-3-azabicyclo[3.1.0]hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 11),

N-{[(1α, 5α, 6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0] hexane-3-carboxylic acid (4-trifluoromethyl-phenyl)-amide (Compound No.12),

N-{[(1α,5α,6α)-3-[2-(3,5-Difluoro-phenyl)-acetyl]-3-azabicyclo[3.1.0]hex-6-ylmethyl]}-2-hydroxy-2-cyclopentyl-2-phenyl acetamide (Compound No. 13),

N-{[(1α,5α,6α)-3-(4-Tert-butylbenzenesulfonyl)-3-azabicyclo[3.1.0]hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 14),

N-{[(1α, 5α, 6α)-3-(2-Fluorobenzoyl)-3-azabicyclo [3.1.0]hex-6-ylmethyl}]-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 15),

N-{[(1α, 5α, 6α)-3-(3,4,5-Trimethoxybenzoyl)-3-azabicyclo [3.1.0]hex-6-yl methyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 16),

N-{[(1α, 5α, 6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0] hexane-3-carboxylic acid (4-fluorophenyl)-amide (Compound No.17),

N-{[(1α, 5α, 6α)-3-Phenylacetyl-3-azabicyclo [3.1.0] hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 18),

N-{[(1α, 5α, 6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid-4-nitro-benzyl ester (Compound No. 19),

N-{[(1α, 5α, 6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid isobutyl ester (Compound No. 20),

N-{[(1α, 5α, 6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 4-nitro-phenyl ester (Compound No. 21),

N-{[(1α, 5α, 6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid benzyl ester (Compound No. 22),

N-{[(1α, 5α, 6α)-3-(4-Fluorobenzenesulphonyl)-3-azabicyclo [3.1.0] hex-6-yl methyl}]-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 23),

N-{[(1α, 5α, 6α)-3-(2,4,6-Trisopropylbenzenesulphonyl)-3-azabicyclo [3.1.0] hex-6-yl methyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 24),

N-{[(1α, 5α, 6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0] hexane-3-carboxylic acid allylamide (Compound No.25),

N-{[(1α, 5α, 6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0] hexane-3-carboxylic acid (2,4-dimethoxy-phenyl)-amide (Compound No.26),

N-{[(1α, 5α, 6α)-3-(3,5-Dimethylbenzoyl)-3-azabicyclo [3.1.0] hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No.27),

N-{[(1α, 5α, 6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0] hexane-3-carboxylic acid (4-benzyloxy-phenyl)-amide (Compound No.28),

N-{[(1α, 5α, 6α)-3-Chloro-3-azabicyclo [3.1.0] hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 29),

N-{[(1α, 5α, 6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0] hexane-3-carboxylic acid amide (Compound No.30),

N-{[(1α, 5α, 6α)-3-Cyano-3-azabicyclo [3.1.0] hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 31),

N-{[(1α, 5α, 6α)-3-Chloro-3-azabicyclo [3.1.0] hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide hydrochloride salts (Compound No. 32),

N-{[(1α, 5α, 6α)-3-Chloro-3-azabicyclo [3.1.0] hex-6-ylmethyl]}-2-cyclohexyl-2-hydroxy-2-phenyl acetamide (Compound No. 33),

N-{[(1α, 5α, 6α)-3-Chloro-3-azabicyclo [3.1.0] hex-6-ylmethyl]}-2-hydroxy-2-diphenyl acetamide (Compound No. 34),

N-{[(1α, 5α, 6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 9H-fluoren-9-ylmethyl ester (Compound No.35),

N-{[(1α, 5α, 6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid butyl ester (Compound No.36),

N-{[(1α, 5α, 6α)-3-(Methanesulphonyl)-3-azabicyclo [3.1.0] hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 37),

N-{[(1α, 5α, 6α)-6-{[(2-Cyclopentyl-2-hydroxy-2-phenyl-acetylamino)-methyl]}-3-aza-bicyclo[3.1.0] hexane-3-carboxylic acid (2,4-difluoro-phenyl)-amide (Compound No.38),

N-{[(1α, 5α, 6α)-3-(4-Methoxybenzoyl)-3-azabicyclo [3.1.0] hex-6-ylmethyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No. 39),

N-{[(1α, 5α, 6α)-3-(3-Benzo[1,3]-dioxol-5-yl-propionyl)-3-azabicyclo [3.1.0] hex-6-yl methyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No.40),

N-{[(1α, 5α, 6α)-3-(Dimethylsulfamoyl)-3-azabicyclo [3.1.0] hex-6-yl methyl]}-2-cyclopentyl-2-hydroxy-2-phenyl acetamide (Compound No.41).

their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, stereoisomers or polymorphs.

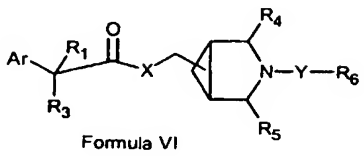
48. A pharmaceutical composition comprising a therapeutically effective amount of a compound as defined in claim 1 together with pharmaceutically acceptable carriers, excipients or diluents.

49. A method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory, urinary and gastrointestinal systems, wherein the disease or disorder is mediated through muscarinic receptors, comprising administering to said animal or human, a therapeutically effective amount of a compound having the structure of Formula I of claim 1.

50. The method according to claim 49, wherein the disease or disorder is urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes or gastrointestinal hyperkinesis.

51. The method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory, urinary and gastrointestinal systems, wherein the disease or disorder is mediated through muscarinic receptors, comprising administering to said animal or human, a therapeutically effective amount of the pharmaceutical composition according to claim 48.

52. A process of preparing a compound of Formula VI



Formula VI

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, stereoisomers or polymorphs,

wherein

R_1 is hydrogen, lower (C_1-C_6) alkyl, lower (C_2-C_7) alkenyl, lower (C_2-C_7) alkynyl, cycloalkyl, amino, substituted amino, -OR_z {wherein R_z is selected from hydrogen, -$Si(CH_3)_3$, lower (C_1-C_6) alkyl, lower (C_2-C_6) alkenyl, lower (C_2-C_6) alkynyl, cycloalkyl, aryl, and -C(=O)NHR_r (wherein R_r is selected from hydrogen, lower (C_1-C_6) alkyl, lower (C_2-C_6) alkenyl, lower (C_2-C_6) alkynyl, aryl, and cycloalkyl)};

R_3 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, and heteroarylalkyl;

R_4 and R_5 are independently selected from hydrogen, lower (C_1-C_6) alkyl, lower (C_2-C_7) alkenyl, and lower (C_2-C_7) alkynyl;

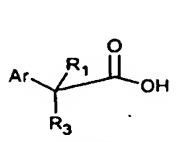
R_6 is selected from alkyl, alkenyl, alkynyl, cycloalkyl, -NR_pR_q (wherein R_p and R_q are selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, and heteroarylalkyl), aryl, aralkyl, heteroaryl, heterocyclyl, heterocyclylalkyl, and heteroarylalkyl, or R_p and R_q may also together join to form a heterocyclyl ring;

X is oxygen, -NR_7 (wherein R_7 is selected from hydrogen, lower (C_1-C_6) alkyl, lower (C_2-C_7) alkenyl, lower (C_2-C_7) alkynyl, aralkyl, and aryl; and

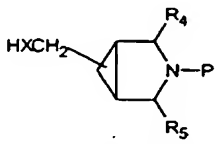
Ar is aryl, heteroaryl, and heterocyclyl,

the process comprising:

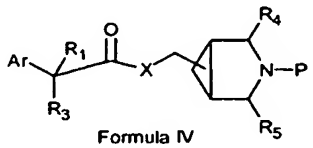
a) condensing a compound of Formula II (wherein Ar, R_1 and R_3 are the same as defined earlier) with a compound of Formula III (wherein X, R_4 and R_5 are the same as defined earlier and P is a protecting group) to give a compound of Formula IV,



Formula II

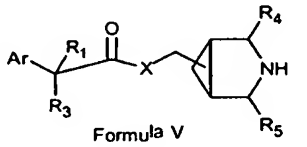


Formula III



Formula IV

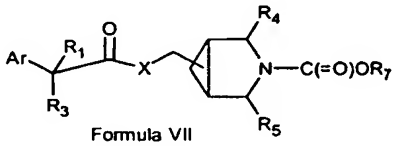
b) deprotecting the compound of Formula IV to give a compound of Formula V, and



Formula V

c) reacting the compound of Formula V with a compound of Formula L-Y-R_6 (wherein L is a leaving group, Y is –C(=O), SO_2 and R_6 is the same as defined earlier) to give a compound of Formula VI.

53. A process of preparing a compound of Formula VII



Formula VII

wherein

R_1 is hydrogen, lower (C_1-C_6) alkyl, lower (C_2-C_7) alkenyl, lower (C_2-C_7) alkynyl, cycloalkyl, amino, substituted amino, -OR_z {wherein R_z is selected from hydrogen, -$Si(CH_3)_3$, lower (C_1-C_6) alkyl, lower (C_2-C_6) alkenyl, lower (C_2-C_6) alkynyl, cycloalkyl, aryl, and -C(=O)NHR_r (wherein R_r is selected from hydrogen, lower (C_1-C_6) alkyl, lower (C_2-C_6) alkenyl, lower (C_2-C_6) alkynyl, aryl, and cycloalkyl)};

R_3 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, and heteroarylalkyl;

R_4 and R_5 are independently selected from hydrogen, lower (C_1-C_6) alkyl, lower (C_2-C_7) alkenyl, and lower (C_2-C_7) alkynyl;

R_6 is selected from alkyl, alkenyl, alkynyl, cycloalkyl, $-NR_pR_q$ (wherein R_p and R_q are selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, and heteroarylalkyl), aryl, aralkyl, heteroaryl, heterocyclyl, heterocyclylalkyl, and heteroarylalkyl, or R_p and R_q may also together join to form a heterocyclyl ring;

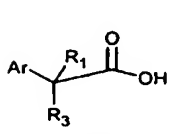
R_7 is selected from hydrogen, lower (C_1-C_6) alkyl, lower (C_2-C_7) alkenyl, lower (C_2-C_7) alkynyl, aralkyl, and aryl;

X is oxygen, $-NR_7$ (wherein R_7 is as defined above); and

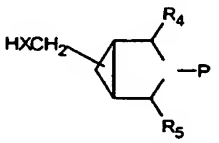
Ar is aryl, heteroaryl, and heterocyclyl,

the process comprising:

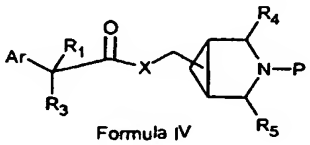
a) condensing a compound of Formula II (wherein Ar, R_1 and R_3 are the same as defined earlier) with a compound of Formula III (wherein X, R_4 and R_5 are the same as defined earlier and P is a protecting group) to give a compound of Formula IV,



Formula II

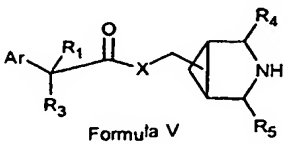


Formula III



Formula IV

b) deprotecting the compound of Formula IV to give a compound of Formula V, and

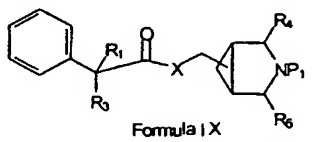


Formula V

reacting the compound of Formula V with a compound of Formula

hal–C(=O)OR_7 (wherein R_7 is the same as defined earlier and hal is halogen) to give a compound of Formula VII.

54. A process of preparing a compound of Formula IX



Formula IX

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, stereoisomers or polymorphs, wherein

R_1 is hydrogen, lower (C_1-C_6) alkyl, lower (C_2-C_7) alkenyl, lower (C_2-C_7) alkynyl, cycloalkyl, amino, substituted amino, -OR_z {wherein R_z is selected from hydrogen, -$Si(CH_3)_3$, lower (C_1-C_6) alkyl, lower (C_2-C_6) alkenyl, lower (C_2-C_6) alkynyl, cycloalkyl, aryl, and -C(=O)NHR_r (wherein R_r is selected from hydrogen, lower (C_1-C_6) alkyl, lower (C_2-C_6) alkenyl, lower (C_2-C_6) alkynyl, aryl, and cycloalkyl)};

R_3 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, and heteroarylalkyl;

R_4 and R_5 are independently selected from hydrogen, lower (C_1-C_6) alkyl, lower (C_2-C_7) alkenyl, and lower (C_2-C_7) alkynyl;

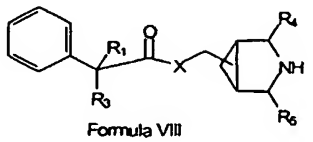
R_7 is selected from hydrogen, lower (C_1-C_6) alkyl, lower (C_2-C_7) alkenyl, lower (C_2-C_7) alkynyl, aralkyl, and aryl;

X is oxygen, or -NR_7 (wherein R_7 is as defined above); and

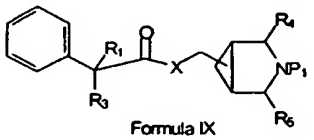
P_1 is halogen (F, Cl, Br or I), cyano or –C(=O)OR_7 (R_7 is the same as defined earlier)

the process comprising:

N-protecting the compound of Formula VIII to give a compound of Formula IX



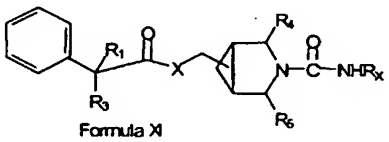
Formula VIII



Formula IX

[wherein P_1 is halogen (F, Cl, Br or I), cyano or $-C(=O)OR_7$ (R_7 is the same as defined earlier)].

55. A process of preparing a compound of Formula XI



Formula XI

wherein,

R_1 is hydrogen, lower (C_1-C_6) alkyl, lower (C_2-C_7) alkenyl, lower (C_2-C_7) alkynyl, cycloalkyl, amino, substituted amino, $-OR_z$ {wherein R_z is selected from hydrogen, $-Si(CH_3)_3$, lower (C_1-C_6) alkyl, lower (C_2-C_6) alkenyl, lower (C_2-C_6) alkynyl, cycloalkyl, aryl, and $-C(=O)NHR_r$ (wherein R_r is selected from hydrogen, lower (C_1-C_6) alkyl, lower (C_2-C_6) alkenyl, lower (C_2-C_6) alkynyl, aryl, and cycloalkyl)};

R_3 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, and heteroarylalkyl;

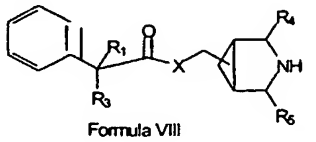
R_4 and R_5 are independently selected from hydrogen, lower (C_1-C_6) alkyl, lower (C_2-C_7) alkenyl, and lower (C_2-C_7) alkynyl;

X is oxygen, or $-NR_7$ (wherein R_7 is as defined above); and

R_x is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, aryl, aralkyl, $S(O)_2R_6$ {wherein R_6 is R_6 is selected from alkyl, alkenyl, alkynyl, cycloalkyl, $-NR_pR_q$ (wherein R_p and R_q are selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, and heteroarylalkyl), aryl, aralkyl, heteroaryl, heterocyclyl, heterocyclylalkyl, and heteroarylalkyl, or R_p and R_q may also together join to form a heterocyclyl ring}, heteroaryl, heterocyclyl, heteroarylalkyl, and heterocyclylalkyl,

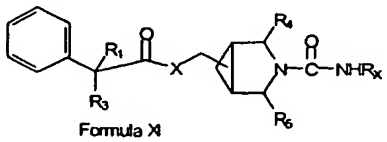
the process comprising

reacting a compound of Formula VIII with a compound of Formula X



Formula VIII

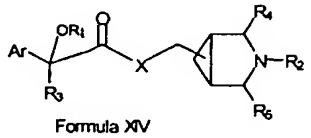
Formula X



Formula XI

(wherein R_x is the same as defined earlier) to give a compound of Formula XI.

56. A process of preparing a compound of Formula XIV



Formula XIV

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, stereoisomers or polymorphs, wherein,

R_2 is carboxy, $-SO_2R_6$ {wherein R_6 is selected from alkyl, alkenyl, alkynyl, cycloalkyl, $-NR_pR_q$ (wherein R_p and R_q are selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, and heteroarylalkyl), aryl, aralkyl, heteroaryl, heterocyclyl, heterocyclylalkyl, and heteroarylalkyl, or R_p and R_q may also together join to form a heterocyclyl ring}, $-C(=O)OR_7$ (wherein R_7 is selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and aralkyl), $-C(=O)NR_xR_y$ (wherein R_x and R_y are each independently selected from hydrogen, hydroxy (as restricted by the definition that both R_x and R_y cannot be hydroxy at the same time), alkyl, alkenyl, alkynyl, aryl, aralkyl, $S(O)_2R_6$ wherein R_6 is the same as defined above, heteroaryl, heterocyclyl, heteroarylalkyl, and heterocyclylalkyl, or R_x and R_y may also together join to form a heterocyclyl ring), acyl, halogen (F, Cl, Br, I), cyano, -

NR_xR_y, wherein R_x and R_y are the same as defined above), or $-C(=O)CH_2OR_x$ (wherein R_x is the same as defined above);

R_3 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, and heteroarylalkyl;

R_4 and R_5 are independently selected from hydrogen, lower (C_1-C_6) alkyl, lower (C_2-C_7) alkenyl, and lower (C_2-C_7) alkynyl;

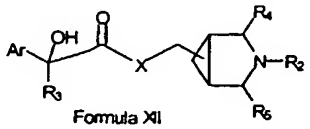
R_t is alkyl;

X is oxygen, $-NR_7$ (wherein R_7 is selected from hydrogen, lower (C_1-C_6) alkyl, lower (C_2-C_7) alkenyl, lower (C_2-C_7) alkynyl, aralkyl, and aryl; and

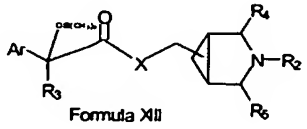
Ar is aryl, heteroaryl, and heterocyclyl

which comprises:

a) reacting a compound of Formula XII with trimethyl silyl chloride to give a compound of Formula XIII, and



Formula XII



Formula XIII

b) O-alkylating the compound of Formula XIII to give a compound of Formula XIV.

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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Published:
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MUSCARINIC RECEPTOR ANTAGONISTS

(57) Abstract: This present invention generally relates to muscarinic receptor antagonists, which are useful, among other uses, for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems mediated through muscarinic receptors. The invention also relates to the process for the preparation of disclosed compounds, pharmaceutical compositions containing the disclosed compounds, and the methods for treating diseases mediated through muscarinic receptors.

WO 2006/035282 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2005/002838

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/439

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBASE, BIOSIS, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004/069835 A (RANBAXY LABORATORIES LIMITED; MEHTA, ANITA; MIRIYALA, BRUHASPATHY; KUM) 19 August 2004 (2004-08-19) cited in the application the whole document	1-56
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
22 February 2006	03/03/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Frelon, D

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INTERNATIONAL SEARCH REPORT

Inter al application No
PCT/IB2005/002838

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2005/002838

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 49-51 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter al application No
PCT/IB2005/002838

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